INHIBITORS OF NLRP3

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of, and priority to U.S. Provisional Patent Application No. 63/237,049 filed on August 25, 2021, and U.S. Provisional Patent Application No. 63/311,463 filed on February 18, 2022, the contents of which are herein incorporated by reference in their entirety and for all purposes.

FIELD OF THE INVENTION

The present invention relates to compounds that are useful as inhibitors of NOD-like receptor protein 3 (NLRP3) inflammasome pathway. The present invention also relates to processes for the preparation of said compounds, pharmaceutical compositions comprising said compounds, methods of using said compounds in the treatment of various diseases and disorders, and medicaments containing them, and their use in diseases and disorders mediated by NLRP3.

BACKGROUND

The term of inflammasome was coined by Martinon et al. to describe the molecular platform triggering activation of inflammatory caspases and processing of interleukin 1 (IL-1) family cytokines (Fabio Martinon et al., *Mol Cell* 10(2):417-26, 2002). Inflammasomes are part of the innate immune system. Inflammasome activation is initiated by assembling of a multiprotein complex, including nucleotide binding oligomerization domain (NOD)-like receptor (NLR), the adapter apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and the effector protease caspase-1. The assemble of the complex results in the activation of caspase-1 and the release of the mature proinflammatory cytokines, such as IL-1β and IL-18.

Among inflammasomes, the NLR family NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome has been studied extensively and was found to be activated by a wide spectrum of stimuli. The regulatory mechanisms of NLRP3 activation are summarized in a recent review paper (Seungwha Paik et al., *Cell Mol Immunol* 18(5):1141-1160, 2021).

NLRP3 activation is triggered by various infectious, non- infectious molecules, including molecular byproducts of aging, physical inactivity and overnutrition. Once activated, it boosts

the downstream production of the inflammatory cytokines IL-1β and IL-18. Gain-of function mutations of NLRP3 are associated with several genetic disorders including cryopyrin-associated periodic syndromes (CAPS). Additionally, NLRP3 is implicated in numerous common I) autoimmune,II) autoinflammatory, III) neurodegenerative, IV) cardiovascular and V) neuromuscular and muscular degenerative diseases e.g. (Matthew S J Mangan et al., *Nat Rev Drug Discov* 17(8):588-606, 2018; Corcoran et al., *Pharmacol Rev* 73(3):968-1000, 2021; Dubuisson et al., *Cells* 10(11):3023, 2021). Inflammasome activation has also been identified in retinal pigment epithelium (RPE) cells and proposed to be a causal factor for RPE dysfunction and degeneration (Gao et al., *Mediators Inflamm* 2015:690243, 2015). Further, NLRP3 activation is associated with severe COVID-19 cases and cytokine release syndrome (CRS) caused by cell-based therapeutics and biologic treatments (Tracey L Freeman and Talia H Swartz *Front Immunol* 11:1518, 2020; Lin et al., *PLoS Pathog* 6;15(6):e1007795, 2019).

Therefore, an NLRP3 inflammasome inhibitor could be used as a single or combination of agents clinically as novel therapies for these diseases. Thus, there is a need for inhibitors of the NLRP3 inflammasome pathway to provide new and/or alternative treatments for these inflammasome-related diseases, disorders , such as autoinflammatory fever syndrome cryopyrin-associated periodic syndrome (CAPS), sickle cell disease, chronic liver disease, nonalcoholic steatohepatitis (NASH), gout, hyperoxaluria, pseudogout (chondrocalcinosis), Type I/Type II diabetes and related complications (e.g. nephropathy, retinopathy), fibrosis, rheumatoid arthritis, inflammatory bowel diseases, asthma and allergic airway inflammation, neuroinflammation-related disorders (e.g. multiple sclerosis, brain infection, acute injury, , Alzheimer's disease, Parkinson's disease, Huntington's disease), neuromuscular and muscular degenerative diseases, atherosclerosis and cardiovascular risk (e.g. cardiovascular risk reduction (CvRR), hypertension), hidradenitis suppurativa, wound healing and scar formation, and cancer (e.g. colon cancer, lung cancer, myeloproliferative neoplasms, leukemias, myelodysplastic syndromes (MDS), myelofibrosis).

References:

Fabio Martinon, Kimberly Burns, Jürg Tschopp The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta *Mol Cell* 10(2):417-26, 2002.

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Matthew S J Mangan, Edward J Olhava, William R Roush, H Martin Seidel, Gary D Glick, Eicke Latz Targeting the NLRP3 inflammasome in inflammatory diseases *Nat Rev Drug Discov* 17(8):588-606, 2018

Sarah Corcoran, Reena Halai, Matthew A Coope Pharmacological Inhibition of the Nod-Like Receptor Family Pyrin Domain Containing 3 Inflammasome with MCC950 *Pharmacol Rev* 73(3):968-1000, 2021

Nicolas Dubuisson, Romain Versele, María A Davis-López de Carrizosa, Camille M Selvais, Sonia M Brichard, Michel Abou-Samra Walking down Skeletal Muscle Lane: From Inflammasome to Disease Cells 10(11):3023, 2021

Jiangyuan Gao, Ruozhou Tom Liu, Sijia Cao, Jing Z Cui, Aikun Wang, Eleanor To, Joanne A Matsubara NLRP3 inflammasome: activation and regulation in age-related macular degeneration *Mediators Inflamm* 2015:690243, 2015

Tracey L Freeman and Talia H Swartz Targeting the NLRP3 Inflammasome in Severe COVID-19 *Front Immunol* 11:1518, 2020

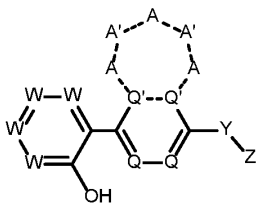
Lan Lin, Lei Xu, Weihua Lv, Li Han, Yaozu Xiang, Lei Fu, Meilin Jin, Rui Zhou, Huanchun Chen, Anding Zhang An NLRP3 inflammasome-triggered cytokine storm contributes to Streptococcal toxic shock-like syndrome (STSLS) *PLoS Pathog* 6;15(6):e1007795, 2019

SUMMARY OF THE INVENTION

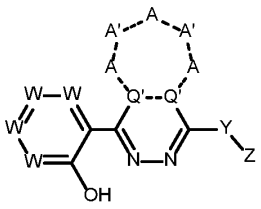
The invention provides compounds or pharmaceu-tically acceptable salts thereof, pharmaceutical compositions thereof, which compounds inhibit the NLRP3 inflammasome pathway. The invention further provides methods of treating, or preventing, disease and/or disorders related to NLRP3, comprising administering to a subject in need thereof an effective amount of the compounds of the invention, or a pharmaceutically acceptable salt thereof.

Various aspects of the invention are described herein.

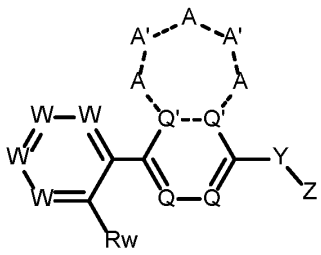
The instant application discloses a compound of Formulae Ia, Ib, Ic, or Id:



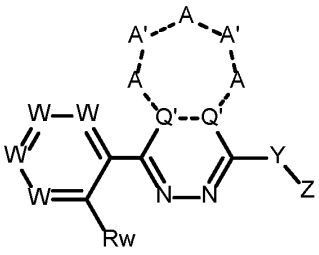
Ia



Ib



Ic



Id

wherein:

R_w is hydrogen, $C_{1\text{-}6}$alkyl (e.g., CH_3), $C_{2\text{-}8}$alkynyl, halogen (e.g., F, Cl), $C_{1\text{-}6}$alkoxy (e.g., OCH_3), halo-$C_{1\text{-}4}$alkyl (e.g., CHF_2, CF_3), halo-$C_{1\text{-}4}$alkoxy (e.g., $OCHF_2$, OCF_3), cyano, $-NH_2$, $-N(C_{1\text{-}6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1\text{-}6}alkyl)_2$, $-S(=O)(C_{1\text{-}6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, NR_{1b}, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)NR_{1b}$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2$

or $S(=O)_2NR_{1b}$, wherein each C_{1-6}alkyl, heterocycle (e.g., 2, 5-dihydrofuran-3-yl), heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each Q is independently N or CH;

each Q' is independently N, C or CH;

each A is independently CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each A' is independently absent, CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each R_a is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR_2$, =O, $=N-OR_2$, $-SR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-N(R_2)_2$, $-NR_2S(=O)(=NR_2)R^2$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)OR_2$, $-OC(=O)OR_2$, $-C(=O)N(R_2)_2$, $-OC(=O)N(R_2)_2$, $-NR_2C(=O)R_2$, $-P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo-C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each---represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b}, or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl, C_{3-10}cycloalkyl, C_{2-7}heterocycloalkyl or aryl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each R' is independently heterocyclyl, heteroaryl, aryl, C_{3-8}cycloalkyl, C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl (e.g., trifluoromethyl, difluoromethyl), halo-C_{1-4}alkoxy (e.g., trifluoromethoxy), hydroxy-C_{1-4}alkyl, halogen, hydroxy or cyano,

wherein each heterocyclyl (e.g., 1-methyl-2,5-dihydro-1H-pyrrol-3-yl, 2,5-dihydrofuran-3-yl, 3,6-dihydro-2H-pyran-3-yl, 3,6-dihydro-2H-pyran-4-yl, 5,6-dihydro-2H-pyran-3-yl, N-methyl pyrrol-3-yl, N-pyrrolidin-1-yl, pyrrolidin-3-yl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, N-methyl pyridinone-4-y,), heteroaryl (e.g., 1,2,3-triazol-1-yl, 1,2,3,-triazol-2-yl, 1,2-pyrazol-4-yl, 5-methyl-1,2,4-thiadiazol-2-yl, N-methyl pyrrol-3-yl, N-methyl pyridinone-4-yl, tetrazol-5-yl), C_{3-8}cycloalkyl (2-cyanocycloprop-1-yl, cyclopropyl) and aryl (e.g., phenyl, 4-chloro-2-cyanophenyl, 4-chloro-2-hydroxyphenyl) are optionally substituted with 1, or 2 substituents each selected from R_3;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, C_{1-6}alkoxy, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl, C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

with the proviso that the compound is not Phenol, 5-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-2-[4-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-1-naphthalenyl]; 5-[Phenyl(6-phenyl-4-dibenzothienyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzothienyl)amino]-1-naphthalenyl]phenol; 5-[2-Dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-[2-Dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-(4-Dibenzofuranylphenylamino)-2-[4-(4-dibenzofuranylphenylamino)-1-naphthalenyl]phenol; 5-(4-Dibenzofuranyl-2-naphthalenylamino)-2-[4-(4-dibenzofuranyl-2-naphthalenylamino)-1-naphthalenyl]phenol; 5-[Phenyl(6-phenyl-4-dibenzofuranyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzofuranyl)amino]-1-naphthalenyl]phenol; 5-([1,1′-Biphenyl]-2-yl-4-dibenzofuranylamino)-2-[4-([1,1′-biphenyl]-2-yl-4-dibenzofuranylamino)-1-naphthalenyl]phenol; 4-[4-(4-Dibenzofuranylphenylamino)-1-naphthalenyl]-2′,3′,5′,6′-tetrafluoro-4′-(2-naphthalenylphenylamino)[1,1′-biphenyl]-3-ol; 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]phenol; or 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]-4-fluorophenol; and

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

The invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the definition of the compound of Formulae I-XI,

or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. The pharmaceutical composition is useful in the treatment of diseases and/or disorders related to the NLRP3 activity. In another aspect, the invention provides a combination, in particular a pharmaceutical combination, comprising a therapeutically effective amount of a compound according to the definition of compounds of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents. In another aspect, the invention provides a combination, in particular a pharmaceutical combination, as disclosed herein, for use as a medicament.

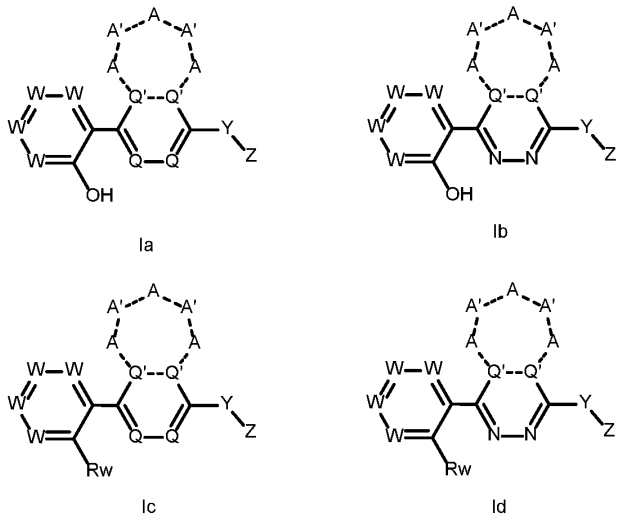
In another aspect, the invention provides a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder in which the NLRP3 signaling contributes to the pathology, and/or symptoms, and/or progression, of said disease or disorder. In another aspect, the invention provides a method of treating a disease or disorder in which the NLRP3 signaling contributes to the pathology, and/or symptoms, and/or progression, of said disease or disorder, comprising administering a therapeutically effective amount of a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof. In another aspect, the invention provides a method of inhibiting the NLRP3 inflammasome activity in a subject in need thereof, the method comprises administering to the subject in need thereof a therapeutically effective amount of a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof. Another aspect of the invention, relates to the use of a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, as a medicament.

Another aspect of the invention, relates to a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

Another aspect of the invention, also provides a compound of Formulae I-XI, or subFormulae thereof, as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder selected from inflammasome-related disease/disorders, immune diseases, inflammatory diseases, auto-immune diseases, and auto-inflammatory diseases.

DETAILED DESCRIPTION OF THE INVENTION

An aspect of the invention provides a compound having the structure of Formulae Ia, Ib, Ic, or Id:



wherein:

R_w is hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}8}$alkynyl, halogen, $C_{1\text{-}6}$alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, cyano, $-NH_2$, $-N(C_{1\text{-}6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1\text{-}6}alkyl)_2$, $-S(=O)(C_{1\text{-}6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$, $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each $C_{1\text{-}6}$alkyl, heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each Q is independently N or CH;

each Q' is independently N, C or CH;

each A is independently CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each A' is independently absent, CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each R_a is independently H, deuterium, halogen, -CN, -OH, -OR_2, =O, =N-OR_2, -SR_2, -$S(=O)R_2$, -$S(=O)_2R_2$, -$N(R_2)_2$, -$NR_2S(=O)(=NR_2)R^2$, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)OR_2$, -$OC(=O)OR_2$, -$C(=O)N(R_2)_2$, -$OC(=O)N(R_2)_2$, -$NR_2C(=O)R_2$, -$P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each---represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b}, or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl, C_{3-10}cycloalkyl, C_{2-7}heterocycloalkyl or aryl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each R' is independently heterocyclyl, heteroaryl, aryl, C_{3-8}cycloalkyl, C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkyl, halogen, hydroxy or cyano,

wherein each heterocycle, heteroaryl, C_{3-8}cycloalkyl and aryl are optionally substituted with 1, or 2 substituents each selected from R_3;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, C_{1-6}alkoxy, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl, C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, $(halo\text{-}C_{1-6}alkyl)_2$-amino, hydroxy-$C_{1-4}$alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-

amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

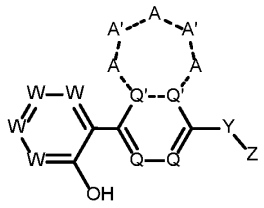
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

with the proviso that the compound is not Phenol, 5-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-2-[4-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-1-naphthalenyl]; 5-[Phenyl(6-phenyl-4-dibenzothienyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzothienyl)amino]-1-naphthalenyl]phenol; 5-[2-Dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-[2-

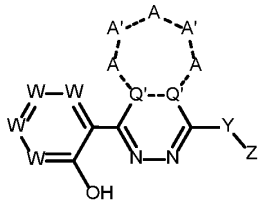
Dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-(4-Dibenzofuranylphenylamino)-2-[4-(4-dibenzofuranylphenylamino)-1-naphthalenyl]phenol; 5-(4-Dibenzofuranyl-2-naphthalenylamino)-2-[4-(4-dibenzofuranyl-2-naphthalenylamino)-1-naphthalenyl]phenol; 5-[Phenyl(6-phenyl-4-dibenzofuranyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzofuranyl)amino]-1-naphthalenyl]phenol; 5-([1,1′-Biphenyl]-2-yl-4-dibenzofuranylamino)-2-[4-([1,1′-biphenyl]-2-yl-4-dibenzofuranylamino)-1-naphthalenyl]phenol; 4-[4-(4-Dibenzofuranylphenylamino)-1-naphthalenyl]-2′,3′,5′,6′-tetrafluoro-4′-(2-naphthalenylphenylamino)[1,1′-biphenyl]-3-ol; 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]phenol; or 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]-4-fluorophenol; and

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

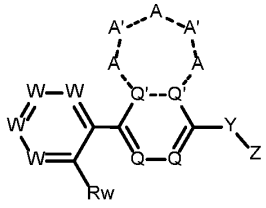
Another aspect of the invention provides a compound having the structure of Formulae IIa, IIb, IIc, or IId:



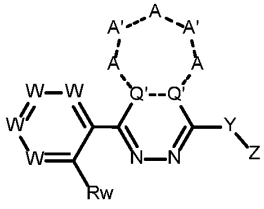
IIa



IIb



IIc



IId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, -NH_2, -$N(C_{1-6}alkyl)_2$, thiol, -SO_2NH_2, -$SO_2N(C_{1-6}alkyl)_2$, -S(=O)(C_{1-6}alkyl), cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each C_{1-6}alkyl, heterocycle, heteroaryl and aryl are optionally substituted with 1or 2 substituents each selected from R_5;

each W is independently CH, CR' or N, wherein at least one Q' is N;

each Q is independently N or CH;

each Q' is independently N, C or CH;

each A is independently CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each A' is independently absent, CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each R_a is independently H, deuterium, halogen, -CN, -OH, $-OR_2$, =O, =N-OR_2, $-SR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-N(R_2)_2$, $-NR_2S(=O)(=NR_2)R^2$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)OR_2$, $-OC(=O)OR_2$, $-C(=O)N(R_2)_2$, $-OC(=O)N(R_2)_2$, $-NR_2C(=O)R_2$, $-P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each-- represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl, C_{3-10}cycloalkyl, C_{2-7}heterocycloalkyl or aryl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each R' is independently heterocyclyl, heteroaryl, aryl, C_{3-8}cycloalkyl, C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkyl, halogen, hydroxy or cyano,

wherein each heterocycle, heteroaryl, C_{3-8}cycloalkyl and aryl are optionally substituted with 1, or 2, substituents each selected from R_3;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, C_{1-6}alkoxy, NH(hydroxyl-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each

Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl, C_{3-10}cycloalkyl a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or$_2$substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R' and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

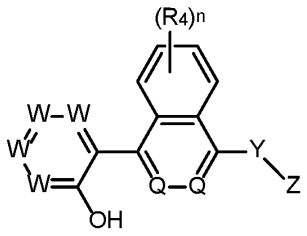
wherein heterocyclyl is a saturated or partially unsaturated$_{3-6}$membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

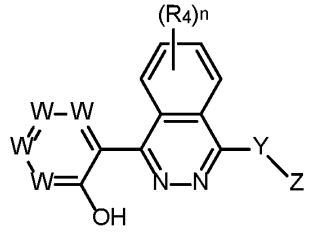
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

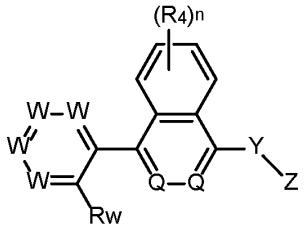
Another aspect of the invention provides a compound having the structure of Formulae IIIa, IIIb, IIIc, or IIId:



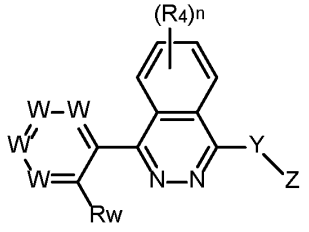
IIIa



IIIb



IIIc



IIId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$,

$NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each Q is independently N, or CH;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}$alkyl$)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}$alkyl$)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl$)_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl,

C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R' and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S,

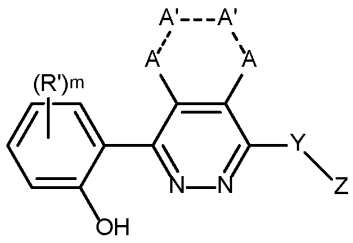
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

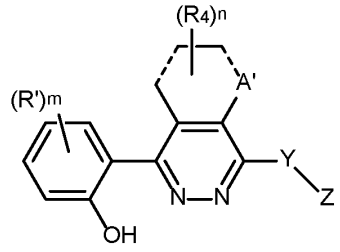
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

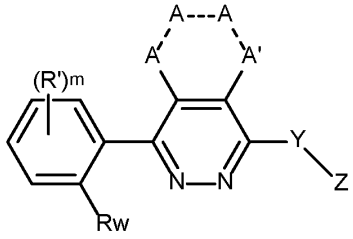
Another aspect of the invention provides a compound having the structure of Formulae IVa, IVb, IVc, or IVd:



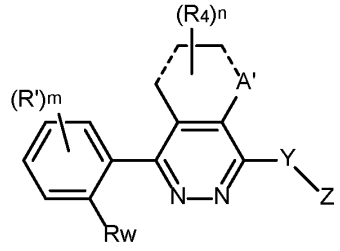
IVa



IVb



IVc



IVd

wherein:

R_w is hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}8}$alkynyl, halogen, $C_{1\text{-}6}$alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, cyano, $-NH_2$, $-N(C_{1\text{-}6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1\text{-}6}alkyl)_2$, $-S(=O)(C_{1\text{-}6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5 each A is independently NH, S, O, CH_2, or CR_4;

A' is independently NH, S, O, CH_2, CR_4 or absent;

Each --represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

R_{1a} is hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl;

R_{1b} is hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocycle, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

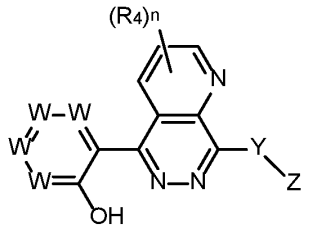
m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

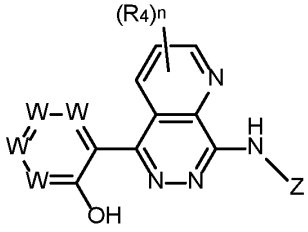
wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides a compound having the structure of Formulae

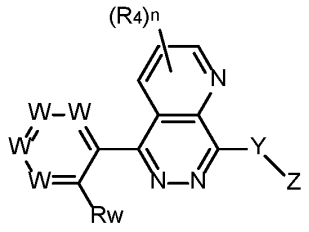
Va, Vb, Vc, or Vd:



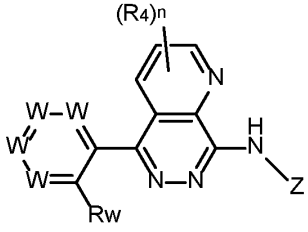
Va



Vb



Vc



Vd

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

R_{1a} is hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl;

R_{1b} is hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein

heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system,

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R' or R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

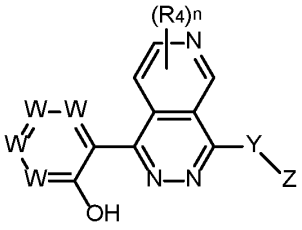
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

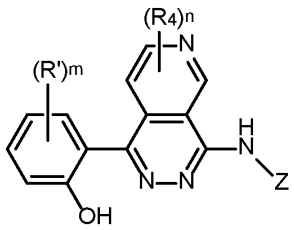
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

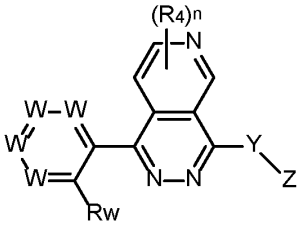
Another aspect of the invention provides a compound having the structure of Formulae VIa, VIb, VIc, or VId:



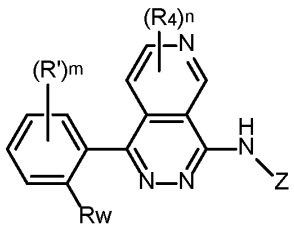
VIa



VIb



VIc



VId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$,

$NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)NHR_{1b}$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-$C_{1-6}alkyl)_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R'or R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

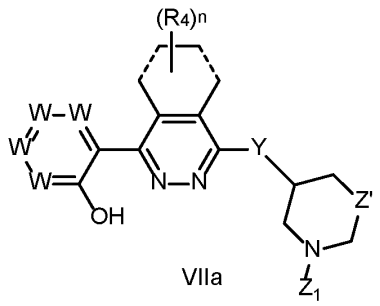
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

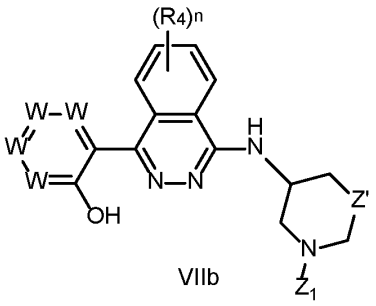
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

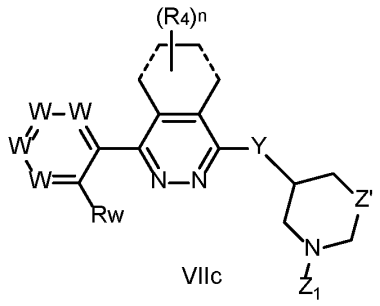
Another aspect of the invention provides a compound having the structure of Formulae VIIa, VIIb, VIIc, or VIId:



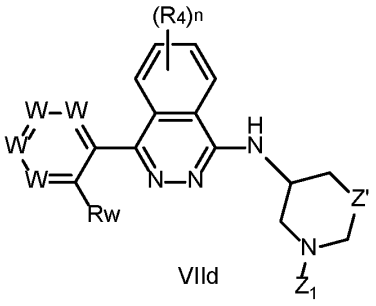
VIIa



VIIb



VIIc



VIId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each-- represents either an absent, single, or double bond;

each Z' is independently CH_2 or absent;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxy-C_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl; and

each Z_1, R', and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

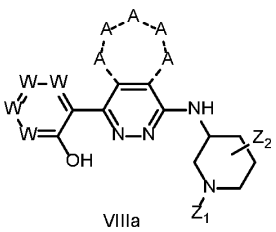
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

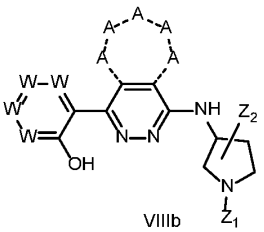
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

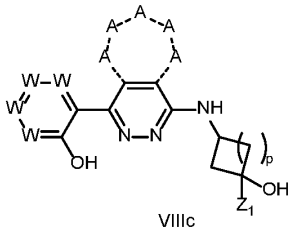
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides a compound having the structure of Formulae VIIIa, VIIIb, VIIIc, VIIId, VIIIe, or VIIIf:


VIIIa


VIIIb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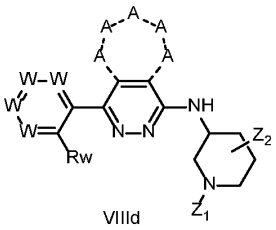
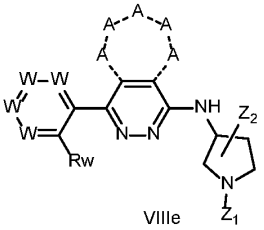
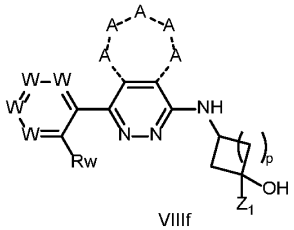

VIIId


VIIIe


VIIIf

wherein

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, -NH_2, -$N(C_{1-6}alkyl)_2$, thiol, -SO_2NH_2, -$SO_2N(C_{1-6}alkyl)_2$, -$S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each A is independently absent, CH, CH_2, CR_a, CHRa, N, NH, NR_a, S, or O, wherein C and N may optionally be substituted with R_4;

each R_a is independently H, deuterium, halogen, -CN, -OH, -OR_2, =O, =N-OR_2, -SR_2, -$S(=O)R_2$, -$S(=O)_2R_2$, -$N(R_2)_2$, -$NR_2S(=O)(=NR_2)R^2$, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)OR_2$, -$OC(=O)OR_2$, -$C(=O)N(R_2)_2$, -$OC(=O)N(R_2)_2$, -$NR_2C(=O)R_2$, -$P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each-- represents either an absent, single, or double bond;

p is 0, 1, 2, 3 or 4;

each Z_1, Z_2, R_2, R' or R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl;

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

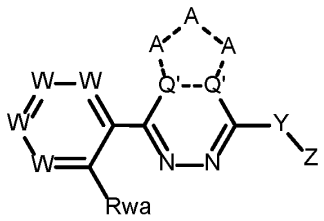
wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkylamino, $(C_{1-4}alkyl)_2$amino, aminoC_{1-4}alkyl, hydroxylC_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides a compound having the structure of Formula IXa:



IXa

wherein:

each W is independently CH, CR' or N;

each Q' is independently N, or C, wherein at least one Q' is N;

each A is independently CH, CH_2, CR_a, CR_4, N, NH or NR_4;

Y is NR_{1b} or a bond;

each R_{wa} is hydrogen, hydroxyl, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy,

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-$C_{1-6}alkyl)_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxyl-Chydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system,

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

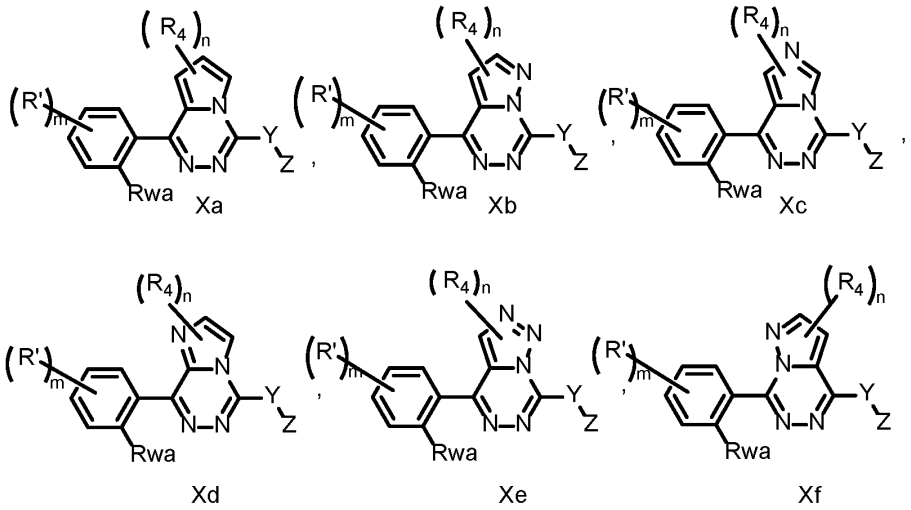
R' is selected from H, substituted or unsubstituted cycloalkyl, halo-C_{1-4}alkyl, haloalkoxy, halogen, C_{1-6} alkoxy, cyano, hydroxy-C_{1-4}alkyl or aryl optionally substituted by C_{1-4}alkyl;

each R_a is independently H, deuterium, halogen, -CN, -OH, $-OR_2$, =O, =N-OR_2, $-SR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-N(R_2)_2$, $-NR_2S(=O)(=NR_2)R^2$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)OR_2$, $-OC(=O)OR_2$, $-C(=O)N(R_2)_2$, $-OC(=O)N(R_2)_2$, $-NR_2C(=O)R_2$, $-P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl; and

R_4 is independently selected from halogen, hydroxyl, cyano, or C_{1-4}alkyl;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides a compound having the structure of Formulae Xa,, Xb, Xc, Xd, Xe or Xf:



wherein:

each R_{wa} is hydrogen, hydroxyl, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy

R' is selected from hydrogen, halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

R_4 is selected from hydrogen, C_{1-4} alkyl, halogen, halo-C_{1-4}alkyl;

Y is NR_{1b} or a bond;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxy-C_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-$C_{1-6}alkyl)_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or$_2$substituents each selected from R_3; and

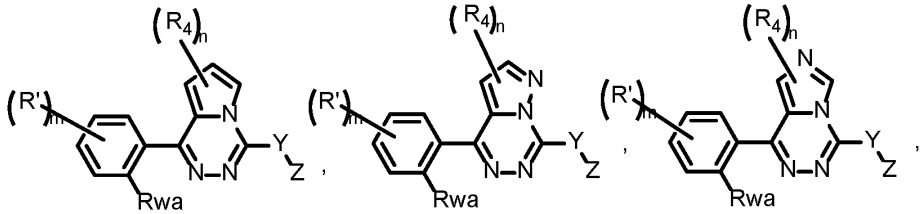
R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

m is 0, 1, 2, 3, or 4; and

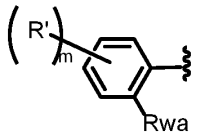
n is 0, 1, 2, or 3;

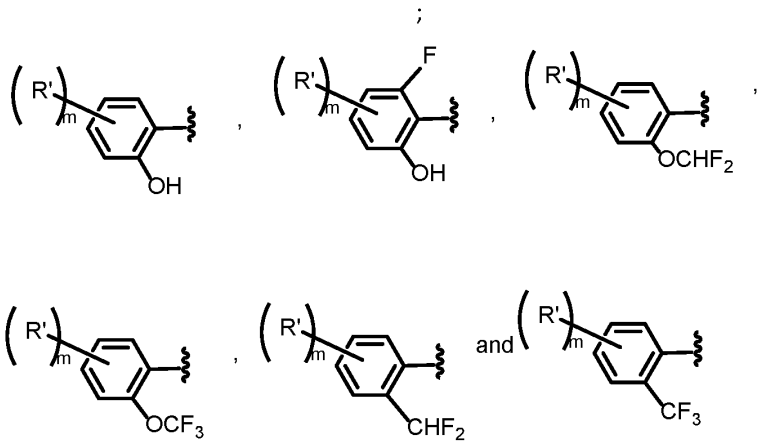
wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides a compound having the structure of Formulae XIa, XIb, XIc:



XIa XIb XIc

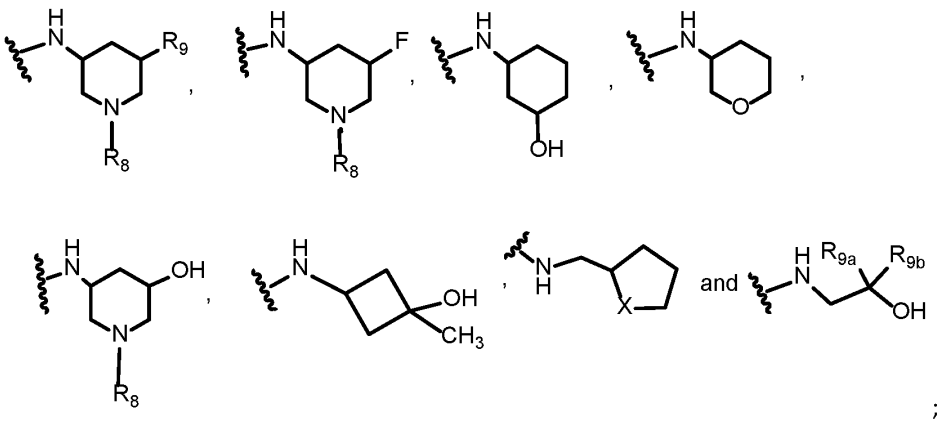
wherein the moiety having the structure  is selected from:



;

R' is selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy and C_{3-10}cycloalkyl;

Y and Z when taken together is selected from:



;

R_4 is selected from hydrogen, C_{1-4} alkyl, halogen, halo-C_{1-4}alkyl;

R_8 is selected from C_{1-4}alkyl, CH_2CH_2OH, $CH_2CH_2OCF_3$, $CH_2CH_2OCHF_2$ and $CH_2CH_2C(CH_3)_2OH$;

R_9, R_{9a}, R_{9b} is selected from hydrogen or C_{1-4}alkyl and C_{3-6}cycloalkyl, wherein C_{9a} and C_{9b} can optionally cyclized to form a 3-6 membered ring;

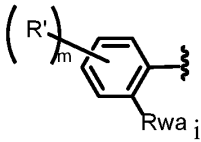
m is 0, 1, 2, 3, or 4;

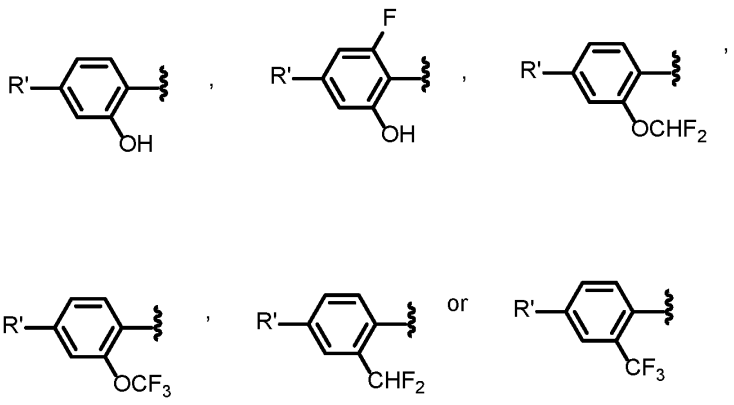
n is 0, 1, 2, or 3; and

X is selected from O or NR_8;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

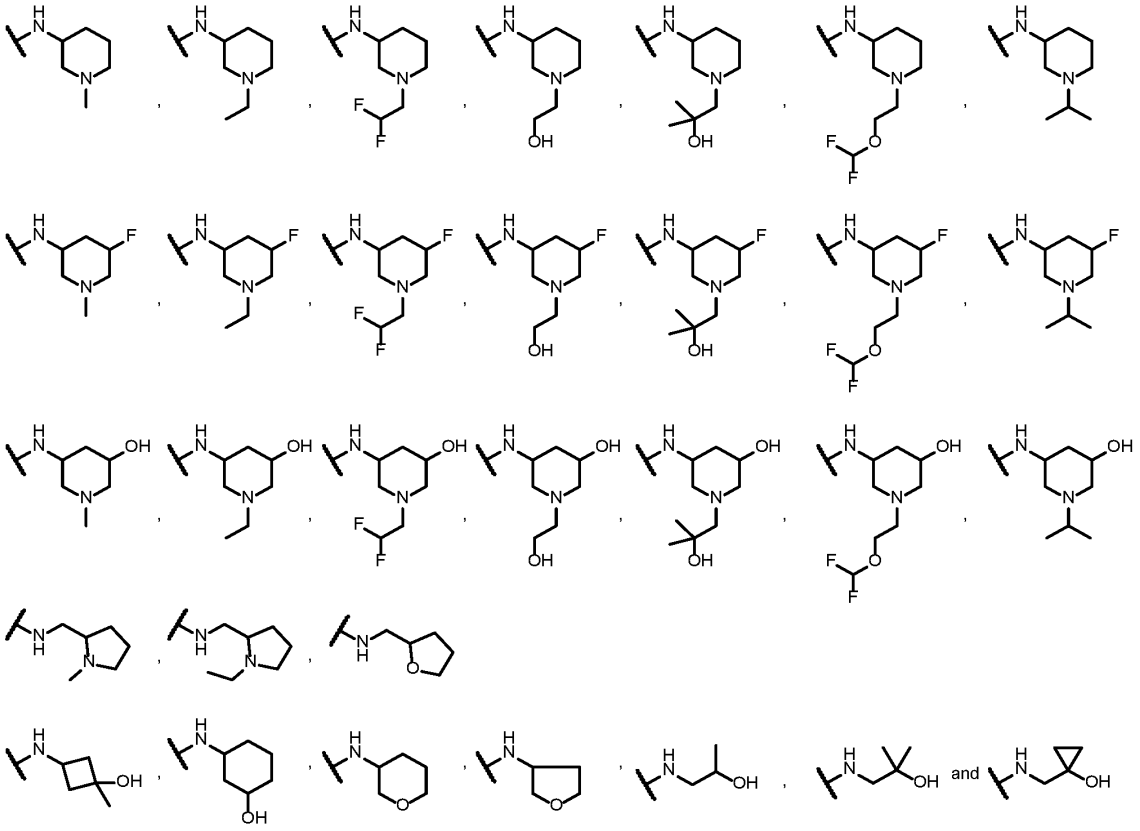
Another aspect of the invention provides a compound having the structure of Formulae XIa, XIb, XIc:

wherein the moiety having the structure  is selected from:



wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect includes a compound of Formulae I-XI, wherein Y and Z when taken together is selected from:



;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

Another aspect of the invention provides any one of the compounds selected from the following:

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}thieno[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol;

2-{4-[(pyrrolidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)benzene-1,3-diol;

5-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-methyl-4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

3-hydroxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)benzonitrile;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpyrrolidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-fluoro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(piperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-(5-methyl-1,2,4-thiadiazol-3-yl)-2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1H-1,2,3-triazol-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(5-methyl-1,2,4-thiadiazol-3-yl)phenol;

4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)[1,1'-biphenyl]-3-ol;

3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)[1,1'-biphenyl]-4-ol;

4,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2,3-dimethyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(1-methylpiperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(7,7-dimethyl-4-{[(3R)-piperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7,7-dimethyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{methyl[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-fluoro-3-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(5,6-dihydro-2H-pyran-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol;

2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-(3,6-dihydro-2H-pyran-4-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(2,5-dihydrofuran-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-chloro-2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(oxolan-3-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol;

1-[3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]ethan-1-one;

ethyl [(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-methoxy-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

4-hydroxy-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridine-2-carbonitrile;

3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-6-(trifluoromethyl)pyridin-2-ol;

2-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-cyclopropyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-methyl-3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-2-ol;

5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-2-(trifluoromethyl)pyridin-4-ol;

6-hydroxy-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridine-2-carbonitrile;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

2-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

4-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

3-hydroxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(pyrrolidin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methyl-1H-pyrrol-3-yl)phenol;

2-{4-[(1-methylazepan-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]methyl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]methyl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

[(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetic acid;

5-methyl-2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)phenol;

2-{1-[(piperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(1-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethoxy)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-chloro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methylpyrrolidin-3-yl)phenol;

2-(4-{[2-(morpholin-4-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(azetidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-[1-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[2-(piperidin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-[1-(4-methylpiperazin-1-yl)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol;

2-(4-methyl-5-{[(3R)-1-methylpiperidin-3-yl]amino}-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazin-8-yl)-5-(trifluoromethyl)phenol;

2-{1-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

4-[2-amino-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]methanesulfonamide;

4-[2-(methylamino)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]acetamide;

4-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-(4-chloro-2-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)benzonitrile;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;

1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-chloro-2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-hydroxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

3,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-chloro-3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-N-[(3R)-1-methylpiperidin-3-yl]-1H-pyrazolo[3,4-d]pyridazin-7-amine;

1-[2-(2,5-dihydrofuran-3-yl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(1-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}-1H-pyrazolo[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-[4-({2-[(3R)-3-methylmorpholin-4-yl]ethyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({2-[(3S)-3-methylmorpholin-4-yl]ethyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[2-(piperazin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(azetidin-2-yl)methyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{1-[3-(dimethylamino)piperidin-1-yl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-(piperazin-1-yl)pyrido[3,4-d]pyridazine;

2-(1-methyl-8-{[(3R)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(1-methyl-8-{[(3S)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzene-1-sulfonamide;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-[4-cyclopropyl-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-methyl-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-4-ol;

4-(2-methoxy-6-methylpyridin-3-yl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

2-(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

1-{4-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}-N,N-dimethylpiperidin-3-amine;

2-amino-3-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

4-(2,3-difluoro-4-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

3-(difluoromethoxy)-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-[2-(difluoromethoxy)-3-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzene-1-sulfonamide;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-3-ol;

1-[2-(methoxymethoxy)-4-(1,3-oxazol-2-yl)phenyl]-N-[(3S)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(1,3-oxazol-2-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(difluoromethoxy)-5-fluoro-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-{4-[(1-methyl-1H-pyrazol-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzamide;

5-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-8-amine;

8-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-5-amine;

2-{1-[(1-methylazepan-3-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-{2-[(oxetan-3-yl)oxy]-4-(trifluoromethyl)phenyl}pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenyl]methanol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(methanesulfonyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-cyclopropyl-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-3-ol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(4-chloro-2-fluoro-6-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-azabicyclo[2.2.2]octan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(pyrimidin-2-yl)phenol;

1-{4-[2-methoxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}-N,N-dimethylpiperidin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-(trifluoromethyl)pyridin-3-yl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-(2,4,6-trimethylphenyl)pyrido[3,4-d]pyridazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2,4-di(propan-2-yl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-(3-cyclopropyl-6-fluoro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

6-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-chloro-3-fluoro-2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)phenol;

2-{4-[(4-methyl-4-azaspiro[2.5]octan-7-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-cyclobutylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(2,4-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-methyl-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-(4-chloro-2,6-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-cyclopropylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2,2,2-trifluoro-1-[3-hydroxy-4-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenyl]ethan-1-one;

1-(4-chloro-2,6-difluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-fluoro-6-methyl-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-nitrophenol;

2-{4-[(1-methylpiperidin-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

5-(cyclopropylethynyl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-ethynyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(prop-1-yn-1-yl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(prop-1-yn-1-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{1-[(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-{1-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{4-[3-(dimethylamino)piperidin-1-yl]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[4-(difluoromethyl)-2-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

5-(cyclopropyloxy)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(pyridin-3-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

1-(2-cyclopropyl-4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(1-methylpiperidin-2-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

1-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[4-(difluoromethyl)-2-fluorophenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}thieno[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-azepan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{4-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(azepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-(4-methoxy-2-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(3-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-3-methyl[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[3-(2,2-difluoroethyl)cyclobutyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

4-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

2-{1-[(4-methyl-1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(4-methyl-1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(1-methylazepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(1,4-dimethyl-1,4-diazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-5,5-difluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidine-2-carboxylate;

3-methoxy-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzene-1,3-diol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3R)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxetan-3-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(4-cyclopropyl-2-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-methylphenol;

3-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[2-(dimethylamino)-2-methylpropyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethyl)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-[4-(cyclohexylamino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-methyl-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-{2-[(propan-2-yl)oxy]-4-(trifluoromethyl)phenyl}pyrido[3,4-d]pyridazin-4-amine;

2-(4-{methyl[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(3-fluoropropyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[4-methoxy-2-(propan-2-yl)phenyl]-N-[(3S)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{methyl[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-methyl-2-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-(1-^{2}H)cyclobutylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S,4R)-4-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1-methylpiperidin-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({[1-(2-hydroxyethyl)piperidin-4-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

3-fluoro-5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-ethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-oxan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-cyclobutylpiperidin-3-yl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)phenol;

2-(4-{[(3S,4R)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1r,3r)-3-hydroxy-3-methylcyclobutyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)-1-methylpiperidine-2-carboxylate;

1-[2-(difluoromethyl)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amin;e

1-[2-(difluoromethyl)-5-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(8-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

N-[(3R)-azocan-3-yl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-methoxy-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(2-methyl-4-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(2-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(2-methyl-4-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

3-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol;

2-(4-{[(6S)-4-methyl-4-azaspiro[2.5]octan-6-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(2-cyclopropyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

2-(2-cyclopropyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methoxyphenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(2-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

3-fluoro-5-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

(1S,3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)cyclohexan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(1R,3S)-3-methoxycyclohexyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-chloro-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

4-[4-bromo-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-oxan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

(1R,3S)-N^1-{1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}cyclohexane-1,3-diamine;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

4-[4-methoxy-2-(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

4-[2,4-bis(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

1-(4-chloro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

(3R,5R)-5-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol;

8-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,2-d][1,2,4]triazin-5-amine;

(3R,5R)-5-{[1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino}-1-methylpiperidin-3-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(2S)-1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-piperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

N-[(3R)-1-ethylpiperidin-3-yl]-1-[4-methoxy-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[4-methyl-2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,2-d][1,2,4]triazin-8-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methoxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)benzonitrile;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-(trifluoromethyl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

4-[4-cyclopropyl-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-5-methyl-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-(trifluoromethoxy)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(2R)-1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-hydroxycyclopentyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3R)-3-hydroxycyclopentyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(3-hydroxy-3-methylcyclohexyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-(trifluoromethyl)phenol;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-[(3R)-3-({1-[4-methoxy-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

5-chloro-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3S)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3S)-oxolan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methyl-1,2,3,6-tetrahydropyridin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2,3]triazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-oxan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[(3R)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]-2-methylpropan-2-ol;

1-[2-(difluoromethoxy)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1r,3r)-3-({1-[2-(difluoromethoxy)-4-methoxyphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxolan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[(3R)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]-2-methylpropan-2-ol;

3,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3S,4S)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3S,4R)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-(oxolan-3-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-[(3R)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

(2R)-1-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-cyclopropyl-3-fluoro-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

3-fluoro-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-[($^{2}H_{3}$)methyloxy]-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

1-[4-bromo-2-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[4-chloro-2-(difluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[4-cyclopropyl-2-(difluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

5-cyclopropyl-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-5-[($^{2}H_3$)methyloxy]-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-[($^{2}H_3$)methyloxy]phenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluoro-5-methylphenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(oxolan-3-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-chloro-2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(1S,3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)cyclohexan-1-ol;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(8-fluoro-4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-2-methylpropan-2-ol;

(1s,3s)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-methyl-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-cyclopropyl-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-2-methylpropan-2-ol;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-methylphenol;

5-cyclopropyl-3-fluoro-2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(6-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(7-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

4-[2-(benzyloxy)-4-bromophenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-oxan-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-chloro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-5-methoxy-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(4-{[(3R)-1-(1-hydroxypropan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluoro-5-methoxyphenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-chloro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

3-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-oxolan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

5-ethyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-{4-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-(2-methoxy-2-methylpropyl)pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(1s,3s)-3-({1-[2,4-bis(difluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R,5S)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol;

5-chloro-2-(4-{[(3S)-oxolan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol;

5-cyclopropyl-2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluorophenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethoxy)phenol;

4-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-cyclopropyl-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{[(3S)-oxolan-3-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{[(3R)-oxolan-3-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-7-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(8-fluoro-4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-fluoro-4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-fluoro-4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

(3R,5R)-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

5-cyclopropyl-2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

(3R,5R)-5-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-ethylpiperidin-3-ol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(3R,5R)-1-ethyl-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-3-ol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-methyl-5-(trifluoromethyl)phenol;

3-fluoro-2-(7-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-{[(2S)-oxolan-2-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-{[(2R)-oxolan-2-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2,4-bis(difluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-(difluoromethoxy)-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-(difluoromethoxy)-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-(difluoromethoxy)-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-(difluoromethoxy)-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(oxolan-2-yl)methyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

5-bromo-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methoxyphenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methylphenol;

5-methoxy-2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

(R)-2-(4-((1-ethylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3,5-dimethylphenol;

(3S,5R)-5-((1-(2-fluoro-6-hydroxy-4-methylphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-methylpiperidin-3-ol;

(3S,5R)-1-ethyl-5-((1-(2-fluoro-6-hydroxy-4-methylphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)piperidin-3-ol;

(3S,5R)-5-((1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-methylpiperidin-3-ol; and

(3S,5R)-5-((1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-ethylpiperidin-3-ol;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

Another aspect of the invention provides any one of the compounds selected from the following:

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(pyrrolidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol hydrochloride;

2-(8-methyl-4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(piperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol hydrochloride;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol diformate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(1-methylpiperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol formate;

2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol N-ethylethanamine;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol diformate;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol formate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)-5-(trifluoromethyl)phenol formate;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol formate;

[(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetic acid formate;

2-{1-[(piperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol hydrochloride;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methylpyrrolidin-3-yl)phenol formate;

2-[1-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

;

2-{1-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-amino-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]methanesulfonamide formate;

4-[2-(methylamino)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]acetamide formate;

1-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-(4-chloro-2-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-N-[(3R)-1-methylpiperidin-3-yl]-1H-pyrazolo[3,4-d]pyridazin-7-amine formate;

2-(1-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}-1H-pyrazolo[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol formate;

2-(1-methyl-8-{[(3R)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol triformate;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile formate;

2-amino-3-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol formate;

4-(2,3-difluoro-4-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzamide formate;

5-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-8-amine formate;

8-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-5-amine formate;

2-{1-[(1-methylazepan-3-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenyl]methanol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-(2,4,6-trimethylphenyl)pyrido[3,4-d]pyridazin-4-amine formate;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidin-1-yl]ethan-1-ol formate;

6-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

6-chloro-3-fluoro-2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

3-methyl-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile formate;

1-(4-chloro-2,6-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2,2,2-trifluoro-1-[3-hydroxy-4-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenyl]ethan-1-one formate;

5-(cyclopropylethynyl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(prop-1-yn-1-yl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(prop-1-yn-1-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-{1-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

5-(cyclopropyloxy)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}amino)piperidin-1-yl]ethan-1-ol formate;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

4-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

1-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

N-[(3R)-azepan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-{4-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-{4-[(azepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(3-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-3-methyl[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(1-methylazepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-{4-[(1,4-dimethyl-1,4-diazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidine-2-carboxylate hydrochloride;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzene-1,3-diol formate;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(1R,3R)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-methylphenol formate;

2-(4-{[2-(dimethylamino)-2-methylpropyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(1-methylpiperidin-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-[4-({[1-(2-hydroxyethyl)piperidin-4-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-ethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

1-(4-chloro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

8-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,2-d][1,2,4]triazin-5-amine formate;

(3R,5R)-5-{[1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino}-1-methylpiperidin-3-ol formate;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-piperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,2-d][1,2,4]triazin-8-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

4-[4-cyclopropyl-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

5-chloro-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3S)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

2-(4-{[(3R)-1-methyl-1,2,3,6-tetrahydropyridin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2,3]triazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3S,4S)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-(difluoromethoxy)-6-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

5-cyclopropyl-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol formate;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol formate;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(6-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-bromo-2-(4-{[(3R)-1-(1-hydroxypropan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

5-cyclopropyl-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol formate;

5-chloro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

5-ethyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol formate;

5-cyclopropyl-2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluorophenol formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(8-fluoro-4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

(3R,5R)-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol formate;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol formate;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate; and

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

wherein a form of the compound is selected from the group consisting of a hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

Another aspect of the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formulae I-XI or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

Another aspect of the invention provides a method for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formulae I-XI.

Another aspect of the invention provides a method of treating or ameliorating a disease modulated by NLRP3 according to claim 15 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease**,** Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated

periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, e.g. Duchenne Muscular Dystrophy (DMD), Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

Another aspect of the invention provides a method of a compound of Formulae I-XI, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

Another aspect of the invention provides a compound Formulae I-XI or a pharmaceutically acceptable salt thereof, for use in treating or ameliorating a disease modulated by NLRP3 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

Another aspect of the invention provides a use of a compound of Formulae I-XI, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

Another aspect of the invention provides a use of a compound Formulae I-XI in the preparation of a pharmaceutical composition for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound or a form thereof in admixture with one or more of the pharmaceutically acceptable excipients.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is selected from H, C_{1-4}alkyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, C_{3-6}cycloalkyl, amino or cyano.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is hydrogen.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is a C_{1-6}alkoxy or halo-C_{1-4}alkoxy.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is $OCHF_2$ or OCF_3.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is OCH_3.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is a C_{1-4}alkyl or halo-C_{1-4}alkyl or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is CH_3.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is c-Pr.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is CF_3 or CHF_2.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is a halogen selected from Br, Cl or F

Another aspect includes a compound of Formulae I-VIII, wherein R_w is F

Another aspect includes a compound of Formulae I-VIII, wherein R_w is Cl.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is Br.

Another aspect includes a compound of Formulae I-VIII, wherein R_w is cyano.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is selected from hydrogen, hydroxyl, C_{1-4}alkyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, C_{3-6}cycloalkyl, amino and cyano.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is hydrogen.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is OH.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is a C_{1-6}alkoxy or halo-C_{1-4}alkoxy.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is $OCHF_2$ or OCF_3.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is OCH_3.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is a C_{1-4}alkyl or halo-C_{1-4}alkyl or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is CH_3.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is c-Pr.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is CF_3 or CHF_2.

Another aspect includes a compound of Formulae IX-XI, wherein Rwa is a halogen selected from Br, Cl or F

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is F

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is Cl.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is Br.

Another aspect includes a compound of Formulae IX-XI, wherein R_{wa} is cyano.

Another aspect includes a compound of Formulae I-III and V-IX, wherein W is selected from CH, CR' and N.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently heterocyclyl, heteroaryl, aryl, cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkoxy, or hydroxy-C_{1-4}alkyl;

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently C_{1-4}alkyl, or halo-C_{1-4}alkyl.

Another aspect includes a compound of Formula I-III and V-X, whereineach R' is independently methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, CF_3, or CHF_2.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently C_{1-4}alkoxy, or deutero-C_{1-4}alkoxy.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently OCH_3, OCD_3, $OCHF_2$, OCF_3, or OEt.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently a halogen, selected from F, Cl, or Br.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently F.

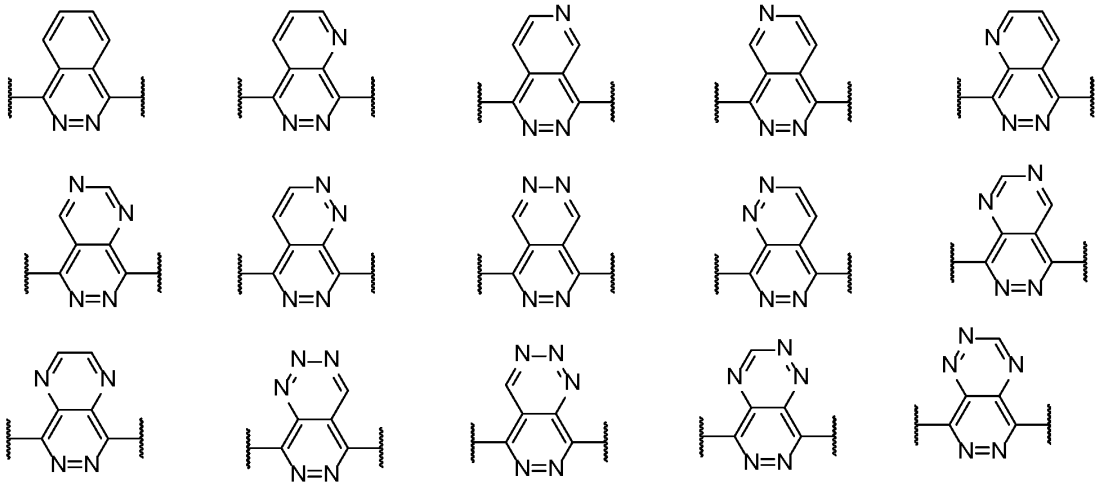
Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently Cl.

Another aspect includes a compound of Formula I-III and V-X, wherein each R' is independently Br.

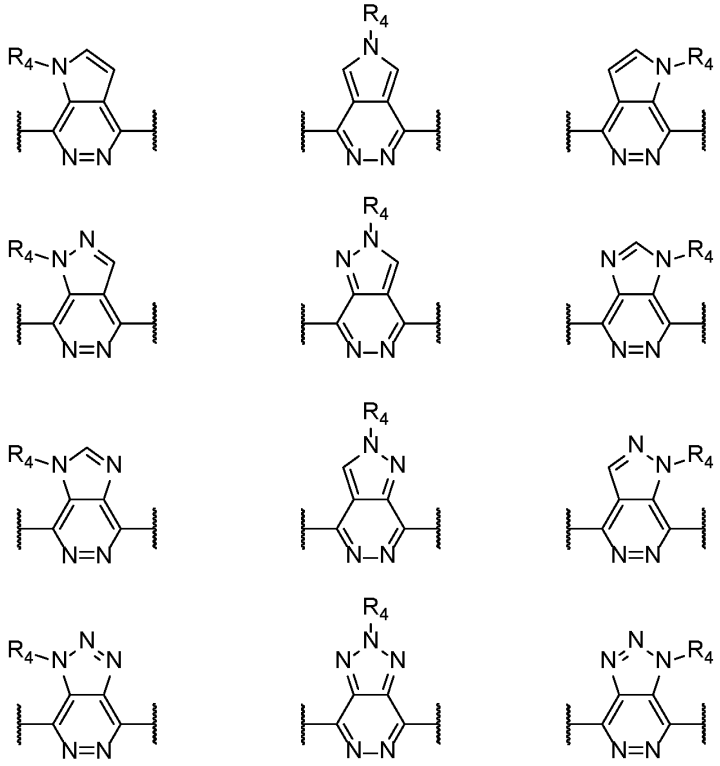
Another aspect includes a compound of Formulae I-III, wherein Q is independently N or CH.

Another aspect includes a compound of Formulae I-III and IX, Q', wherein Q' is independently N, C or CH.

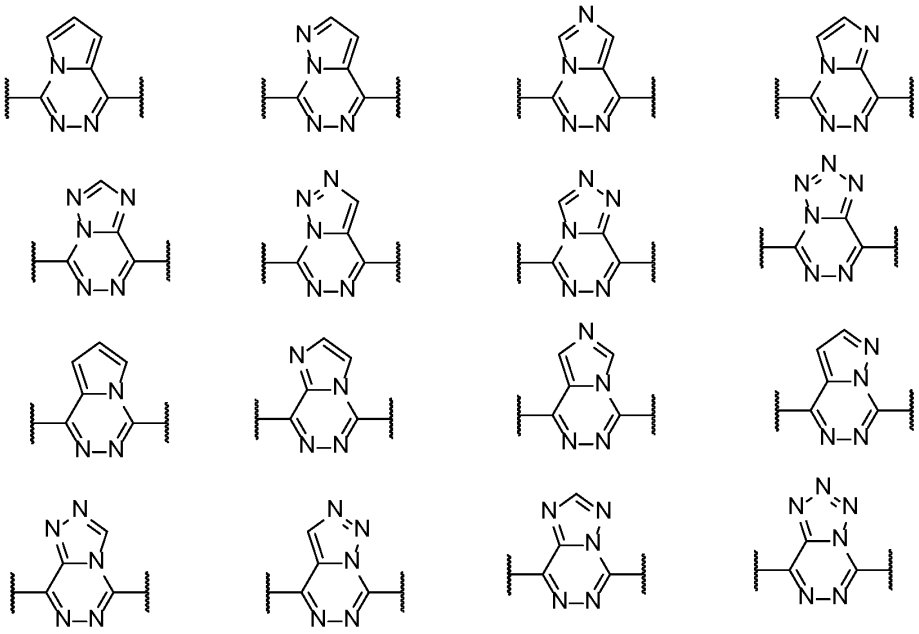
Another aspect of the invention provides that the core of the above Formulae I, and III-VIII may additionally be any of the following structures which may be optionally substituted with oneor more R_4:



Another aspect of the invention provides that the core of the above Formulae I, IV or VIII may additionally be any of the following structures:



Another aspect of the invention provides that the core of Formulae IX-XI may additionally be, but are not limited to, any of the following structures which may be optionally substituted with one or more R_4:



Another aspect includes a compound of Formula I-II, IV, and VIII-IX, wherein each A is independently absent, CH, CH_2, CRa, CHR_a, CR_4, CHR_4, N, NH, NR_4 or NR_a.

Another aspect includes a compound of Formula I-II, IV, and VIII-IX, wherein A' is independently absent, CH, CH_2, CR_a, CHR_a, CHR_4, CHR_a, N, NH, NR_4, NR_a.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a halogen, cyano, C_{1-4}alkyl, C_{3-6}cycloalkyl, haloC_{1-4}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, amino, or C_{1-4}alkylamino.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a halogen selected from F, Cl, or Br.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a cyano.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a C_{1-4}alkyl, which is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or tert-butyl.

Another aspect includes a compound of Formula I-VII, wherein that each R_a is independently a C_{3-6}cycloalkyl, which is selected from cylopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a cyclopropyl, or cyclobutyl.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a C_{1-4}alkoxy or haloC_{1-4}alkoxy, which is selected from methoxy, ethoxy, isopropoxy, cyclopropoxy, difluoromethoxy, and trifluoromethoxy.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently an amino.

Another aspect includes a compound of Formula I-VII, wherein each R_a is independently a C_{1-4}alkylamino, which is selected from methylamino, ethylamino, N, N-dimethylamino, isopropylamino, or cyclopropylamino.

Another aspect includes a compound of Formulae I-XI wherein Y is NR_{1b}.

Another aspect includes that R_{1b} is hydrogen.

Another aspect includes that R_{1b} is a C_{1-4}alkyl, which is selected from methyl, ethyl, propyl, isopropyl, cyclopropyl, or butyl.

Another aspect includes that R1b is methyl.

Another aspect includes a compound of Formulae I-VII and IX-XI, wherein Y is O.

Another aspect includes a compounds of Formulae I-VII and IX-XI, wherein Y is a carbon optionally substituted with R_{1a}.

Another aspect includes a compound of Formula I-VII, wherein R_{1a} is selected from hydrogen, or C_{1-4}alkyl.

Another aspect includes a compound of Formula I-VII, wherein R_{1a} is hydrogen.

Another aspect includes a compound of Formula I-VII, wherein R_{1a} is methyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is C_{3-6}cycloalkyl selected from cyclopropyl, cylcobutyl, cyclopentyl or cyclohexyl, wherein each is optionally substituted with R_2

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclopropyl, optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclopropyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, CHF_2, CF_3, cPr, or cBu.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclobutyl, optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclobutyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, CHF_2, CF_3, cPr, or cBu.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclopentyl, optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclopentyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, CHF_2, CF_3, cPr, or cBu.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclohexyl, optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is cyclohexyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, CHF_2, CF_3, cPr, or cBu.

Another aspect includes a compound of Formulae I-XI, wherein Z is heterocyclyl, wherein each is optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is piperidinyl, tetrahydro-2*H*-pyran, tetrahydrofuran, or pyrrolidinyl, wherein each is optionally substituted with

R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is piperidinyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, iPr, CHF_2, CF_3, cPr, cBu, $-CH_2CH_2OH$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCF_3$, tetrahydrofuranyl, or tetrahydropyranyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is pyrrolidinyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, iPr, CHF_2, CF_3, cPr, cBu, $-CH_2CH_2OH$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCF_3$, tetrahydrofuranyl, or tetrahydropyranyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is tetrahydropyranyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, iPr, CHF_2, CF_3, cPr, cBu, $-CH_2CH_2OH$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCF_3$, tetrahydrofuranyl, or tetrahydropyranyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is tetrahydrofuranyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, iPr, CHF_2, CF_3, cPr, cBu, $-CH_2CH_2OH$, $-CH_2CH_2OCHF_2$, $-CH_2CH_2OCF_3$, tetrahydrofuranyl, or tetrahydropyranyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is C_{1-4}alkyl, optionally substituted with R_2 selected from halogen, cyano, hydroxyl, C_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkyl, haloC_{1-4}alkyl, or C_{3-6}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein Z is C_{1-4}alkyl, optionally substituted with R_2 selected from F, CN, OH, MeO, EtO, iPrO, cPrO, CHF_2O, CF_3O, Me, Et, CHF_2, CF_3, cPr, or cBu.

An aspect of the present description includes a method for preventing, treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is halogen selected from bromo, chloro, fluoro, and iodo.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is fluoro.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is hydroxyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkyl selected from methyl and ethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is ethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is amino

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-6}alkylamino, wherein C_{1-4}alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-6}alkylamino, wherein C_{1-4}alkyl is selected from methyl, ethyl, isopropyl, tert-butyl, 2methylbutyl, and 3-methylpentyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is methylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is ethylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is isopropylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is tert-butylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is 2-methylbutyl-2-amino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is 3-methylpentyl-3-amino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is $(C_{1-6}alkyl)_2$amino, wherein C_{1-4}alkyl is each independently selected from selected from methyl, ethyl, isopropyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is $(C_{1-6}alkyl)_2$amino, wherein C_{1-4}alkyl is methyl or ethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is dimethylamino or diethylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is dimethylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is diethylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is halo-C_{1-4}alkylamino, wherein C_{1-4}alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is halo-C_{1-4}alkylamino, wherein C_{1-4}alkyl is selected from isopropyl and tert-butyl, partially or completely substituted with one or more halogen atoms where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is 1-fluoro-2-methylpropan-2-amino or 1-fluoropropan-2-amino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is hydroxy-C_{1-4}alkylamino, wherein C_{1-4}alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, partially or completely substituted with one or more hydroxy groups where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is hydroxy-C_{1-4}alkylamino, wherein C_{1-4}alkyl is selected from ethyl and propyl, partially or completely substituted with one or more hydroxy groups where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is 2hydroxyethylamino or 3-hydroxypropylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkoxy-C_{1-4}alkyl-amino, wherein C_{1-4}alkoxy is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy, and C_{1-4}alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkoxy-C_{1-4}alkyl-amino, wherein C_{1-4}alkoxy is methoxy and C_{1-4}alkyl is selected propyl, isopropyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is 1methoxypropan-2-amino or 1-methoxy-2-methylpropan-2-amino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkylaminoC_{1-4}alkyl, wherein each C_{1-4}alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkylaminoC_{1-4}alkyl, wherein each C_{1-4}alkyl is independently selected from methyl, ethyl, isopropyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is methylaminomethyl, propan-2-yl-aminomethyl, propan-2-yl-aminoethyl, or tert-butylaminomethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is $(C_{1-4}alkylamino)_2C_{1-4}$alkyl, wherein each C_{1-4}alkyl is independently selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is $(C_{1-4}alkylamino)_2C_{1-4}$alkyl, wherein each C_{1-4}alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is dimethylaminomethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{1-4}alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_2 methoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{3-10}cycloalkyl-amino, wherein C_{3-10}cycloalkyl is selected from cyclopropyl, cylcobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{3-10}cycloalkyl-amino, wherein C_{3-10}cycloalkyl is selected from cyclopropyl, cylcobutyl, cyclopentyl, bicyclo[2.2.1]hexanyl, and adamantyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, wherein C_{3-10}cycloalkyl is selected from cyclopropyl, cylcobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantyl and C_{1-4}alkyl is selected from methyl, ethyl, propyl, and butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, wherein C_{3-10}cycloalkyl is selected from cyclopropyl, cylcobutyl, and cyclopentyl, and C_{1-4}alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is cyclopropylaminomethyl, cyclobutylaminomethyl, or cyclopentylaminomethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heteroaryl-C_{1-4}alkyl-amino, wherein heteroaryl is selected from thienyl, 1*H*pyrazolyl, 1*H*imidazolyl, 1,3thiazolyl, oxazolyl, 1,2,4oxadiazolyl, 1,3,4oxadiazolyl, 1,2,4thiadiazolyl, 1*H*-tetrazolyl, 2*H*-tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, 1,2,4triazinyl, 1,3,5-triazinyl, 1*H*indolyl, 1*H*indazolyl, 2*H*indazolyl, indolizinyl, benzofuranyl, benzothienyl, 1*H*benzimidazolyl, 1,3benzoxazolyl, 1,3benzothiazolyl, 1,3-benzodioxolyl, 1,2,3-benzotriazolyl, 9*H*purinyl, quinolinyl, isoquinolinyl, and quinoxalinyl, and C_{1-4}alkyl is selected from methyl, ethyl, propyl, and butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heteroaryl-C_{1-4}alkyl-amino, wherein heteroaryl is pyridinyl, and C_{1-4}alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is pyridin-2-yl-methylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino, wherein heterocyclyl is selected from azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, 8-azabicyclo[3.2.1]octanyl, and 8oxabicyclo[3.2.1]octanyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino, wherein heterocyclyl is selected from oxetanyl and tetrahydropyranyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is oxetanylamino or tetrahyropyranylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino-C_{1-4}alkyl, wherein heterocyclyl is selected from azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxanyl, 8-azabicyclo[3.2.1]octanyl, and 8oxabicyclo[3.2.1]octanyl, and C_{1-4}alkyl is selected from methyl, ethyl, propyl, and butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino-C_{1-4}alkyl, wherein heterocyclyl is selected from tetrahydrofuranyl, oxanyl, and 8-oxabicyclo[3.2.1]octanyl, and C_{1-4}alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is oxanylaminomethyl, tetrahydrofuranylaminomethyl, and 8-oxabicyclo[3.2.1]octanylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino-C_{3-10}cycloalkyl, wherein heterocyclyl is selected from azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxanyl, 8-azabicyclo[3.2.1]octanyl, and

8oxabicyclo[3.2.1]octanyl, and C_{3-10}cycloalkyl is selected from cyclopropyl, cylcobutyl, cyclopentyl, and cyclohexyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is heterocyclyl-amino-C_{3-10}cycloalkyl, wherein heterocyclyl is oxanyl, and C_{3-10}cycloalkyl is cyclopropyl.

Another aspect includes a compound of Formulae I-XI, wherein R_2 is oxanylaminocyclopropyl.

One aspect includes a compound of Formulae I-XI, wherein R_3 is halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and haloC_{1-4}alkoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_3 is halogen and C_{1-4}alkyl.

Another aspect includes a compound of Formulae I-XI, wherein R_3 is halogen selected from bromo, chloro, fluoro, and iodo.

Another aspect includes a compound of Formulae I-XI, wherein R_3 is fluoro.

Another aspect includes a compound of Formulae I-XI, wherein R_3 is C_{1-4}alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_3 is methyl.

One aspect includes a compound of Formulae I-XI, wherein R_4 is selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkylamino, (C_{1-4}alkyl)$_2$amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl, wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S, wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1 or 2 substituents each selected from R_5.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is selected from halogen, C_{1-4}alkoxy, heteroaryl, and phenyl.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is halogen selected from bromo, chloro, fluoro, and iodo.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is fluoro.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is C_{1-4}alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_4 methoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is heteroaryl, wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S, optionally substituted with 1 or 2 substituents each selected from R_5.

Another aspect includes a compound of Formulae I-XI, wherein R_4 is phenyl, 1 or 2 substituents each selected from R_5.

One aspect includes a compound of Formulae I-XI, wherein R_5 is selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkylamino, $(C_{1-4}alkyl)_2$amino, aminoC_{1-4}alkyl, hydroxylC_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, amino, C_{1-4}alkylamino, aminoC_{1-4}alkyl, hydroxylC_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and C_{3-10}cycloalkyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is halogen selected from bromo, chloro, fluoro, and iodo.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is halogen selected from bromo, chloro and fluoro.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is chloro.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is fluoro.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is hydroxy.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is cyano.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is nitro.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is C_{1-4}alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is deutero-C_{1-4}alkyl wherein C_{1-4}alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and

tert-butyl partially or completely substituted with one or more deuterium atoms where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is ($^2H_3$)methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is amino.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $C_{1\text{-}6}$alkylamino wherein $C_{1\text{-}4}$alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, and 3-methylpentyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $C_{1\text{-}4}$alkylamino wherein $C_{1\text{-}4}$alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is methylamino.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is amino$C_{1\text{-}4}$alkyl wherein $C_{1\text{-}4}$alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is amino$C_{1\text{-}4}$alkyl wherein $C_{1\text{-}4}$alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is aminomethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is hydroxyl$C_{1\text{-}4}$alkyl, wherein $C_{1\text{-}4}$alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl partially or completely substituted with one or more hydroxyl groups where allowed by available valences.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is hydroxyl$C_{1\text{-}4}$alkyl, wherein $C_{1\text{-}4}$alkyl is methyl substituted with one hydroxyl group.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is hydroxymethyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $C_{1\text{-}4}$alkylcarbonyl, wherein $C_{1\text{-}4}$alkyl is selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $C_{1\text{-}4}$alkylcarbonyl, wherein $C_{1\text{-}4}$alkyl is methyl.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $CH_3C(O)$-.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is $C_{1\text{-}4}$alkoxy selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert-butoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_5 methoxy.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is C_{1-4}alkylthio selected from methylthio, ethylthio, propylthio, isopropylthio, butylthio, and tert-butylthio.

Another aspect includes a compound of Formulae I-XI, wherein R_5 methylthio.

Another aspect includes a compound of Formulae I-XI, wherein R_5 is C_{3-10}cycloalkyl selected from cyclopropyl, cylcobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]hexanyl, and adamantly.

Another aspect of the invention provides a method of treating or ameliorating a disease modulated by NLRP3 with a compound of Formulae I-XI wherein said disease is selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, e.g. Duchenne Muscular Dystrophy (DMD), Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

Another aspect of the invention provides a method of treating a subject with a compound of Formulae I-XI, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

Another aspect of the invention provides a compound of Formulae I-XI or a pharmaceutically acceptable salt thereof, for use in treating or ameliorating a disease modulated by NLRP3 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage,

Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

Another aspect of the invention provides a use of a compound of Formulae I-XI, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

Another aspect of the invention provides a use of a compound of Formulae I-XI in the preparation of a pharmaceutical composition for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound or a form thereof in admixture with one or more of the pharmaceutically acceptable excipients.

The application further provides a compound, composition, use or method as described herein.

METHOD OF USE OF THE INVENTION

There is evidence for a role of NLRP3-induced IL-I and IL-18 in the inflammatory responses occurring in connection with, or as a result of, a multitude of different disorders (Menu et al, *Clinical and Experimental Immunology,* 2011, 166, 1-15; Strowig et al, *Nature,* 2012, 481, 278-286). NLRP3 mutations have been found to be responsible for a set of rare autoinflammatory diseases known as CAPS (Ozaki et al, *J. Inflammation Research,* 2015, 8, 15-27; Schroder et al, *Cell,* 2010, 140:821-832; Menu et al, *Clinical and Experimental Immunology,* 2011, 166, 1-15). CAPS are heritable diseases characterized by recurrent fever and inflammation and are comprised of three autoinflammatory disorders that form a clinical continuum. These

diseases, in order of increasing severity, are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile cutaneous neurological articular syndrome (CINCA; also called neonatal-onset multisystem inflammatory disease, NOMID), and all have been shown to result from gain-of-function mutations in the NLRP3 gene, which leads to increased secretion of IL-I beta. NLRP3 has also been implicated in a number of autoinflammatory diseases, including pyogenic arthritis, pyoderma gangrenosum and acne (PAPA), Sweet's syndrome, chronic nonbacterial osteomyelitis (CNO), and acne vulgaris (Cook et al, *Eur J. Immunol.,* 2010, 40, 595-653). A number of autoimmune diseases have been shown to involve NLRP3 including, in particular, multiple sclerosis, type-1 diabetes (TlD), psoriasis, rheumatoid arthritis (RA), Behcet's disease, Schnitzler syndrome, macrophage activation syndrome (Braddock et al. *Nat. Rev. Drug Disc.* 2004, 3, 1-10; Inoue et al, *Immunology,* 2013, 139, 11-18, Coll et al, *Nat. Med.* 2015, 21(3), 248-55; Scott et al, *Clin. Exp. Rheumatol.* 2016, 34(1), 88-93), systemic lupus erythematosus and its complications such as lupus nephritis (Lu et al, *J. Immunol.,* 2017, 198(3), 1119-29), and systemic sclerosis (Artlett et al, *Arthritis Rheum.* 2011, 63(11), 3563-74). NLRP3 has also been shown to play a role in a number of lung diseases including chronic obstructive pulmonary disorder (COPD), asthma (including steroidresistant asthma), asbestosis, and silicosis (De Nardo et al, *Am. J. Pathol.,* 2014, 184: 42-54; Kim et al. *Am. J. Respir Crit Care Med,* 2017, 196(3), 283-97). NLRP3 has also been suggested to have a role in a number of central nervous system conditions, including Multiple Sclerosis (MS), Parkinson's disease (PD), Alzheimer's disease (AD), dementia, Huntington's disease, cerebral malaria, brain injury from pneumococcal meningitis (Walsh et al, *Nature Reviews,* 2014, 15, 84-97; and Dempsey et al. *Brain. Behav. Immun.* 2017, 61, 306-16), intracranial aneurysms (Zhang et al. *J. Stroke and Cerebrovascular Dis.,* 2015, 24, 5, 972-9), and traumatic brain injury (Ismael et al. *J. Neurotrauma.,* 2018, 35(11), 1294-1303). NRLP3 activity has also been shown to be involved in various metabolic diseases including type 2 diabetes (T2D) and its oigan-specific complications, atherosclerosis, obesity, gout, pseudo-gout, metabolic syndrome (Wen et al, *Nature Immunology,* 2012, 13, 352-357; Duewell et al, *Nature,* 2010, 464, 1357-1361; Strowig et al, *Nature,* 2014, 481, 278-286), and non-alcoholic steatohepatitis (Mridha et al. *J. Hepatol.* 2017, 66(5), 1037-46). NLRP3 is also suggested to play a key pathological role in the development and progression of several skeletal muscle diseases, e.g. muscle atrophy, inherited and acquired myopathies (Dubussion et al. *Cells* 2021, 10(11):3023). A role for NLRP3 via IL-I

beta has also been suggested in atherosclerosis, myocardial infarction (van Hout et al. *Eur Heart J.* 2017, 38(11), 828-36), heart failure (Sano et al. *J. Am. Coll. Cardiol.* 2018, 71(8), 875-66), aortic aneurysm and dissection (Wu et al. *Arterioscler Thromb. Vase. Biol.,* 2017, 37(4), 694-706), and other cardiovascular events (Ridker et al, *N. Engl. J. Med,* 2017, 377(12), 1119-31). Other diseases in which NLRP3 has been shown to be involved include: ocular diseases such as both wet and dry age-related macular degeneration (Doyle et al. *Nature Medicine,* 2012, 18, 791-798; Tarallo et al. *Cell* 2012, 149(4), 847-59), diabetic retinopathy (Loukovaara et al. *Acta Ophthalmol.,* 2017, 95(8), 803-8), non-infectious uveitis and optic nerve damage (Puyang et al. *Sci. Rep.* 2016, 6, 20998); liver diseases including non-alcoholic steatohepatitis (NASH) and acute alcoholic hepatitis (Henao-Meija et al, *Nature,* 2012, 482, 179-185); inflammatory reactions in the lung and skin (Primiano et al. *J. Immunol.* 2016, 197(6), 2421-33) including contact hypersensitivity (such as bullous pemphigoid (Fang et al. *J Dermatol Sci.* 2016, 83(2),116-23)), atopic dermatitis (Niebuhr et al. *Allergy,* 2014, 69(8), 1058-67), Hidradenitis suppurativa (Alikhan et al. *J. Am. Acad. Dermatol.,* 2009, 60(4), 539-61), and sarcoidosis (Jager et al. *Am. J. Respir Crit. Care Med.,* 2015, 191, A5816); inflammatory reactions in the joints (Braddock et al, *Nat. Rev. Drug Disc,* 2004, 3, 1-10); amyotrophic lateral sclerosis (Gugliandolo et al. *Int. J. Mol. Sci.,* 2018, 19(7), E1992); cystic fibrosis (larmitti et al. *Nat. Commun.,* 2016,7, 10791); stroke (Walsh et al, *Nature Reviews,* 2014, 15, 84-97); chronic kidney disease (Granata et al. *PLoS One* 2015, 10(3), eoi22272); and inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Braddock et al, *Nat. Rev. Drug Disc,* 2004, 3, 1-10; Neudecker et al. *J. Exp. Med.* 2017, 214(6), 1737-52; Lazaridis et al. *Dig. Dis. Sci.* 2017, 62(9), 2348-56). The NLRP3 inflammasome has been found to be activated in response to oxidative stress. NLRP3 has also been shown to be involved in inflammatory hyperalgesia (Dolunay et al, *Inflammation,* 2017, 40, 366-86). US application US20200361898 in incorporated herein by reference.

DEFINITIONS

To assist in understanding the scope of the compounds of Formulae I-XI or a form thereof described herein, the following Specific Examples are included. The experiments relating to the compounds of Formulae I-XI or a form thereof described herein should not, of course, be construed as specifically limiting the scope of the compounds of Formulae I-XI or a form thereof described herein and such variations of the compounds of Formulae I-XI or a form

thereof as described herein, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope as described herein and hereinafter claimed.

Other than in the working examples, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term "about". Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term "about" in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding techniques.

While the numerical ranges and parameters setting forth the characterization of the compounds of Formulae I-XI or a form thereof described herein are approximations, the numerical values set forth in the working examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

The compounds of Formulae I-XI or a form thereof provided herein are described in more detail with reference to the following non-limiting examples, which are offered to more fully illustrate the scope of the compounds of Formulae I-XI or a form thereof described herein, but are not to be construed as limiting the scope thereof. The examples illustrate the preparation of compounds of Formulae I-XI or a form thereof described herein, and the testing of these compounds of Formulae I-XI or a form thereof *in vitro* and/or *in vivo*. Those of skill in the art will understand that the synthesis techniques described in these examples represent techniques that fall within the practice of those having ordinary skill in the chemical arts, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those having skill in the art should, in light of the present disclosure, appreciate that many changes can

be made in the specific methods that are disclosed herein while still obtaining a like or similar result without departing from the spirit and scope described herein.

In certain embodiments described herein, the compound of Formulae I-XI or a form thereof is isolated for use.

As used herein, the term "isolated" means the physical state of a compound of Formulae I-XI or a form thereof after being isolated and/or separated and/or purified from a synthetic process (*e.g.,* from a reaction mixture) or natural source or combination thereof according to an isolation, separation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.,* chromatography, recrystallization and the like) in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

As used herein, the term "protected" means that a functional group on a compound of Formulae I-XI or a form thereof is in a form modified to preclude undesired side reactions of the functional group when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (2007), Wiley, New York.

Prodrugs and solvates of the compounds of Formulae I-XI or a form thereof described herein are also contemplated.

As used herein, the term "prodrug" means that a functional group on a compound of Formulae I-XI is in a form (*e.g.*, acting as an active or inactive drug precursor) that is transformed *in vivo* to yield an active or more active compound of Formulae I-XI or a form thereof. The transformation may occur by various mechanisms (*e.g.*, by metabolic and/or nonmetabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by V.J. Stella, et. al., "Biotechnology: Pharmaceutical Aspects, Prodrugs: Challenges and Rewards," American Association of Pharmaceutical Scientists and Springer Press, 2007.

In one example, when a compound of Formulae I-XI or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formulae I-XI or a form thereof contains an alcohol

functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a functional group such as alkyl or carbonyloxy and the like. In another example, when a compound of Formulae I-XI or a form thereof contains an amine functional group, a prodrug can be formed by the replacement of one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl.

Pharmaceutically acceptable prodrugs of compounds of Formulae I-XI or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters (e.g., a phosphoramidic acid used to derive a phosphoramidic acid) and mono-, di- or triphosphate esters further substituted with alkyl, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formulae I-XI or a form thereof as a prodrug.

The compounds of Formulae I-XI or a form thereof can form salts, which are intended to be included within the scope of this description. Reference to a compound of Formulae I-XI or a form thereof herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formulae I-XI or a form thereof contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of Formulae I-XI or a form thereof described herein that are safe and effective (*i.e.*, non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formulae I-XI may be formed, for example, by reacting a compound of Formulae I-XI 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.

Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds of Formulae I-XI or a form thereof described herein. Embodiments of acid addition salts include, and are not limited to, acetate, acid phosphate, ascorbate, benzoate,

benzenesulfonate, bisulfate, bitartrate, borate, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, hydrobromide, hydrochloride, dihydrochloride, hydroiodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate, trifluoroacetic acid salt and the like. One or more embodiments of acid addition salts include chloride, hydrochloride, dihydrochloride, trihydrochloride, hydrobromide, acetate, diacetate, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like. More particular embodiments include a chloride, hydrochloride, dihydrochloride, hydrobromide, methanesulfonate, sulfate, trifluoroacetate, trifluoroacetic acid salt and the like.

In certain embodiments of the compounds of Formulae I-XI or a form thereof described herein, the compound is isolated as a salt form, wherein the compound is conjugated with the salt in a ratio represented as, in a non-limiting example, "compound:salt (A:B)," wherein "A" and "B" represent the equivalents of compound to salt in the isolated form.

Additionally, acids which are considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. Certain compounds of Formulae I-XI or a form thereof described herein can also form pharmaceutically acceptable salts with organic bases (for example, organic amines) such as, but not limited to, dicyclohexylamines, *tert*-butyl amines and the like, and with various amino acids such as, but not limited to, arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (*e.g.,* methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, and dibutyl sulfates), long chain halides (*e.g.,*

decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

Compounds of Formulae I-XI, and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formulae I-XI or a form thereof as described herein.

The compounds of Formulae I-XI or a form thereof may contain asymmetric or chiral centers, and, therefore, may exist in different stereoisomeric forms. The present description is intended to include all stereoisomeric forms of the compounds of Formulae I-XI as well as mixtures thereof, including racemic mixtures.

The compounds of Formulae I-XI or a form thereof described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R*/*S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one embodiment, the compounds of Formulae I-XI or a form thereof described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another embodiment, the compounds of Formulae I-XI or a form thereof described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds of Formulae I-XI or a form thereof described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) isomer, as defined by *IUPAC* Nomenclature Recommendations.

As used herein, the term "substantially pure" refers to compounds of Formulae I-XI or a form thereof consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

In one aspect of the description, a compound of Formulae I-XI or a form thereof is a substantially pure (*S*) enantiomer present in an amount greater than or equal to 90%, in an

amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

In one aspect of the description, a compound of Formulae I-XI or a form thereof is a substantially pure (*R*) enantiomer present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

As used herein, the term "racemate" refers to any mixture of isometric forms that are not "enantiomerically pure", including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20, about 85/15 or about 90/10.

In addition, the compounds of Formulae I-XI or a form thereof described herein embrace all geometric and positional isomers. For example, if a compound of Formulae I-XI or a form thereof incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures thereof, are embraced within the scope of the compounds of Formulae I-XI or a form thereof described herein.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of a chiral HPLC column or other chromatographic methods known to those skilled in the art.

Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.,* chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.,* hydrolyzing) the individual diastereomers to the corresponding pure enantiomers.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds of Formulae I-XI or a form thereof (including salts, solvates, esters and prodrugs and transformed prodrugs thereof), which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, diastereomeric and regioisomeric forms,

are contemplated within the scope of the description herein. Individual stereoisomers of the compounds of Formulae I-XI or a form thereof described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described *supra*.

The use of the terms "salt," "solvate," “ester,” "prodrug" and the like, is intended to apply equally to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates, isotopologues or prodrugs of the instant compounds.

One or more compounds of Formulae I-XI or a form thereof described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

As used herein, the term “solvate” means a physical association of a compound of Formulae I-XI or a form thereof described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, “solvate” encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

One or more compounds of Formulae I-XI or a form thereof described herein may optionally be converted to a solvate. Preparation of solvates is generally known. A typical, non-limiting process involves dissolving a compound of Formulae I-XI or a form thereof in a desired amount of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example infrared spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

As used herein, the term “hydrate” means a solvate wherein the solvent molecule is water.

As used herein, the term “isotope enriched” means a compounds of Formulae I-XI or a form thereof which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) or a form thereof described herein include isotopes of hydrogen,

carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as H^2, H^3, C^{13}, C^{14}, N^{15}, O^{18}, O^{17}, P^{31}, P^{32}, S^{35}, F^{18}, Cl^{35} and Cl^{36}, respectively, each of which is also within the scope of this description.

Polymorphic crystalline and amorphous forms of the compounds of Formulae I-XI or a form thereof, and of the salts, solvates, esters and prodrugs of the compounds of Formulae I-XI or a form thereof, are further intended to be included in the scope of the compounds of Formulae I-XI or a form thereof described herein.

TERMINOLOGY

The chemical terms used above and throughout the description herein, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.

As used herein, the term "$C_{1\text{-}8}$alkyl" refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including, without limitation, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like. In some embodiments, $C_{1\text{-}8}$alkyl includes $C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkyl and the like. A $C_{1\text{-}8}$alkyl radical may be optionally substituted where allowed by available valences.

As used herein, the term "aryl" refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, without limitation, phenyl, naphthyl (also referred to as naphthalenyl), anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical may be optionally substituted where allowed by available valences.

As used herein, the term "heteroaryl" refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom, including, without limitation, furanyl, thienyl (also referred to as thiophenyl), pyrrolyl, pyrazolyl (also referred to as 1H-pyrazolyl), imidazolyl (also referred to as 1H-imidazolyl), isoxazolyl (also referred to as 1,2-oxazolyl), isothiazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyranyl, thiopyranyl, pyridinyl (also referred to as pyridyl), pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl (also referred to as 1H-indolyl), azaindolyl, indazolyl (also referred to as 2H-indazolyl), azaindazolyl, isoindolyl, indolizinyl,

benzofuranyl, benzothienyl, benzimidazolyl (also referred to as 1H-benzimidazolyl), benzothiazolyl, benzoxazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl, 9H-purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, acridinyl and the like and associated homologs and regioisomers thereof. A heteroaryl radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

As used herein, the term "heterocyclyl" refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including, without limitation, oxiranyl, oxetanyl, azetidinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, pyrrolinyl, pyrrolidinyl, dihydropyrazolyl, pyrazolinyl, pyrazolidinyl, dihydroimidazolyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, 1,3-dioxolanyl, dihydro-2H-pyranyl, tetrahydro-2H-pyranyl, dihydro-pyridinyl, tetrahydro-pyridinyl, dihydro-pyrimidinyl, tetrahydro-pyrimidinyl, dihydro-pyrazinyl, tetrahydro-pyrazinyl, dihydro-pyridazinyl, tetrahydro-pyridazinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro-triazinyl, tetrahydro-triazinyl, hexahydro-triazinyl, 1,4-diazepanyl, dihydro-indolyl, indolinyl, tetrahydro-indolyl, dihydro-indazolyl, tetrahydro-indazolyl, dihydro-isoindolyl, dihydro-benzofuranyl, tetrahydro-benzofuranyl, dihydro-benzothienyl, tetrahydro-benzothienyl, dihydro-benzoimidazolyl, tetrahydro-benzoimidazolyl, dihydro-benzooxazolyl, tetrahydro-benzooxazolyl, dihydro-benzooxazinyl, tetrahydro-benzooxazinyl, benzo[1,3]dioxolyl (also referred to as 1,3-benzodioxolyl), benzo[1,4]dioxanyl (also referred to as 1,4-benzodioxanyl or 2,3-dihydro-1,4-benzodioxinyl), benzo[1,4]dioxinyl (also referred to as 1,4-benzodioxinyl), 4,5,6,7-tetrahydro-2H-indazolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, dihydro-purinyl, tetrahydro-purinyl, dihydro-quinolinyl, tetrahydro-quinolinyl, dihydro-isoquinolinyl, tetrahydro-isoquinolinyl, dihydro-quinazolinyl, tetrahydro-quinazolinyl, dihydro-quinoxalinyl, tetrahydro-quinoxalinyl

and the like and associated homologs thereof. A heterocyclyl radical may be optionally substituted on a carbon or nitrogen atom ring member where allowed by available valences.

As used herein, the term "halo" or "halogen" generally refers to a halogen atom radical, including fluoro, chloro, bromo and iodo.

As used herein, the term "C_{1-4}alkoxy-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-O-C_{1-4}alkyl.

As used herein, the term "C_{1-4}alkoxy-carbonyl" refers to a radical of the formula: -C(O)-O-C_{1-4}alkyl.

As used herein, the term "C_{1-4}alkoxy-carbonyl-amino" refers to a radical of the formula: -NH-C(O)-O-C_{1-4}alkyl.

As used herein, the term "C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl.

As used herein, the term "(C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl)$_2$.

As used herein, the term "C_{1-4}alkyl-amino-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-NH-C_{1-4}alkyl.

As used herein, the term "(C_{1-4}alkyl)$_2$-amino-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-N(C_{1-4}alkyl)$_2$.

As used herein, the term "C_{1-4}alkyl-amino-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-NH-C_{1-4}alkyl.

As used herein, the term "(C_{1-4}alkyl)$_2$-amino-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-N(C_{1-4}alkyl)$_2$.

As used herein, the term "C_{1-4}alkyl-carbonyl" refers to a radical of the formula: -C(O)-C_{1-4}alkyl.

As used herein, the term "C_{1-4}alkyl-carbonyl-amino" refers to a radical of the formula: -NH-C(O)-C_{1-4}alkyl.

As used herein, the term "C_{1-4}alkyl-thio" refers to a radical of the formula: -S-C_{1-4}alkyl.

As used herein, the term "amino-C_{2-8}alkenyl" refers to a radical of the formula: -C_{2-8}alkenyl-NH_2.

As used herein, the term "amino-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-NH_2.

As used herein, the term "amino-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-NH_2.

As used herein, the term "amino-C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl-NH_2.

As used herein, the term "(amino-C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl-NH_2)$_2$.

As used herein, the term "(amino-C_{1-4}alkyl)(C_{1-4}alkyl)amino" refers to a radical of the formula: -N(C_{1-4}alkyl)(C_{1-4}alkyl-NH_2).

As used herein, the term "amino-C_{2-8}alkynyl" refers to a radical of the formula: -C_{2-8}alkynyl-NH_2.

As used herein, the term "aryl-C_{1-4}alkoxy-carbonyl" refers to a radical of the formula: -C(O)-O-C_{1-4}alkyl-aryl.

As used herein, the term "aryl-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-aryl.

As used herein, the term "aryl-C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl-aryl.

As used herein, the term "(aryl-C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl-aryl)$_2$.

As used herein, the term "aryl-amino" refers to a radical of the formula: -NH-aryl.

As used herein, the term "aryl-amino-carbonyl" refers to a radical of the formula: -C(O)-NH-aryl.

As used herein, the term "benzoxy-carbonyl" refers to a radical of the formula: -C(O)-O-CH_2-phenyl.

As used herein, the term "C_{3-14}cycloalkyl-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-C_{3-14}cycloalkyl.

As used herein, the term "C_{3-14}cycloalkyl-amino" refers to a radical of the formula: -NH-C_{3-14}cycloalkyl.

As used herein, the term "C_{3-14}cycloalkyl-oxy" refers to a radical of the formula: -O-C_{3-14}cycloalkyl.

As used herein, the term " deutero-C_{1-4}alkyl," refers to a radical of the formula: -C_{1-4}alkyl-deutero, wherein C_{1-4}alkyl is partially or completely substituted with one or more deuterium atoms where allowed by available valences.

As used herein, the term "halo-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-halo, wherein C_{1-4}alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.

As used herein, the term "halo-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-halo, wherein C_{1-4}alkyl is partially or completely substituted with one or more halogen atoms where allowed by available valences.

As used herein, the term "halo-C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl-halo.

As used herein, the term "(halo-C_{1-4}alkyl)(C_{1-4}alkyl)amino" refers to a radical of the formula: -N(C_{1-4}alkyl)(C_{1-4}alkyl-halo).

As used herein, the term "(halo-C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl-halo)$_2$.

As used herein, the term "heteroaryl-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-heteroaryl.

As used herein, the term "heteroaryl-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-heteroaryl.

As used herein, the term "heteroaryl-amino" refers to a radical of the formula: -NH-heteroaryl.

As used herein, the term "heterocyclyl-C_{1-4}alkoxy" refers to a radical of the formula: -O-C_{1-4}alkyl-heterocyclyl.

As used herein, the term "heterocyclyl-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-heterocyclyl.

As used herein, the term "heterocyclyl-C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl-heterocyclyl.

As used herein, the term "(heterocyclyl-C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl-heterocyclyl)$_2$.

As used herein, the term "heterocyclyl-amino" refers to a radical of the formula: -NH-heterocyclyl.

As used herein, the term "(heterocyclyl)(C_{1-4}alkyl)amino" refers to a radical of the formula: -N(C_{1-4}alkyl)(heterocyclyl).

As used herein, the term "heterocyclyl-amino-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-NH-heterocyclyl.

As used herein, the term "heterocyclyl-carbonyl" refers to a radical of the formula: -C(O)-heterocyclyl.

As used herein, the term "heterocyclyl-carbonyl-oxy" refers to a radical of the formula: -O-C(O)-heterocyclyl.

As used herein, the term "heterocyclyl-oxy" refers to a radical of the formula: -O-heterocyclyl.

As used herein, the term "hydroxy" refers to a radical of the formula: -OH.

As used herein, the term "hydroxy-C_{1-4}alkoxy-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-O-C_{1-4}alkyl-OH.

As used herein, the term "hydroxy-C_{1-4}alkyl" refers to a radical of the formula: -C_{1-4}alkyl-OH, wherein C_{1-4}alkyl is partially or completely substituted with one or more hydroxy radicals where allowed by available valences.

As used herein, the term "hydroxy-C_{1-4}alkyl-amino" refers to a radical of the formula: -NH-C_{1-4}alkyl-OH.

As used herein, the term "(hydroxy-C_{1-4}alkyl)$_2$-amino" refers to a radical of the formula: -N(C_{1-4}alkyl-OH)$_2$.

As used herein, the term "substituent" means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., "oxo" or "=O") as the point of attachment may be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as the point of attachment to the core structure of Formulae I-XI. A person of ordinary skill in the

art would understand that, while only a single bond is shown, a double bond is intended for those substituents.

As used herein, the term "and the like," with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural isomers), hydration of ring systems (including saturation or partial unsaturation of monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.

As used herein, the term "substituent" means positional variables on the atoms of a core molecule that are attached at a designated atom position, replacing one or more hydrogen atoms on the designated atom, provided that the atom of attachment does not exceed the available valence or shared valences, such that the substitution results in a stable compound. Accordingly, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. It should also be noted that any carbon as well as heteroatom with a valence level that appears to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown.

For the purposes of this description, where one or more substituent variables for a compound of Formulae I-XI encompass functionalities incorporated into a compound of Formulae I-XI, each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.

As used herein, the terms "independently selected," or "each selected" refer to functional variables in a substituent list that may be attached more than once on the structure of a core molecule, where the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent on a core structure for a compound provided herein is understood to include the replacement of the generic substituent with specie substituents that are included within the particular genus, e.g., aryl may be independently replaced with phenyl or naphthalenyl (also referred to as naphthyl) and the like, such that the resulting compound is intended to be included within the scope of the compounds described herein.

As used herein, the term "each instance of" or "each variable is independently" when used in a phrase such as "…aryl, aryl-C_{1-8}alkyl, heterocyclyl and heterocyclyl-C_{1-8}alkyl, wherein

each instance of aryl and heterocyclyl is optionally substituted with one or two substituents…" is intended to include optional, independent substitution on each of the aryl and heterocyclyl rings and on the aryl and heterocyclyl portions of aryl-C_{1-8}alkyl and heterocyclyl-C_{1-8}alkyl.

As used herein, the term "optionally substituted" means that the specified substituent variables, groups, radicals or moieties represent the scope of the genus and may be independently chosen as needed to replace one or more hydrogen atoms on the designated atom of attachment of a core molecule.

As used herein, the terms "stable compound' or "stable structure" means a compound that is sufficiently robust to be isolated to a useful degree of purity from a reaction mixture and Formulaetions thereof into an efficacious therapeutic agent.

As used herein, the terms "subject" and "patient" are used interchangeably to refer to an animal or any living organism having sensation and the power of voluntary movement, and which requires for its existence oxygen and organic food. Nonlimiting examples include members of the human, equine, porcine, bovine, rattus, murine, canine and feline species. In some embodiments, the subject is a mammal or a warm-blooded vertebrate animal. In certain embodiments, the subject is a non-human animal. In specific embodiments, the subject is a human.

Compound names provided herein were obtained using ACD Labs Index Name software provided by ACD Labs and/or ChemDraw Ultra software provided by CambridgeSoft®. When the compound name disclosed herein conflicts with the structure depicted, the structure shown will supercede the use of the name to define the compound intended. Nomenclature for substituent radicals defined herein may differ slightly from the chemical name from which they are derived; one skilled in the art will recognize that the definition of the substituent radical is intended to include the radical as found in the chemical name.

DOSAGE AND ADMINISTRATION

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by other routes of administration including continuous (intravenous drip) topical parenteral,

intramuscular, intravenous, subcutaneous, transdermal (which may include a penetration enhancement agent), buccal, nasal, inhalation and suppository administration, among other routes of administration. The preferred manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the patient's response to the active ingredient.

A compound or compounds of the present invention, as well as their pharmaceutically useable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled in the art will appreciate that an active ingredient can exist in different preparations depending on the target organ or tissue and on the desired dose and pharmacokinetic parameters.

The term “excipient” as used herein refers to a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

“Pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active

component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for parenteral administration (*e.g.*, by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl oleate), and may contain formulating agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually

sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylaza-cycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polyactic acid.

Suitable formulations along with pharmaceutical carriers, diluents and expcipients are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.01 and about 1000 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.1 and about 500 mg/kg body weight, more preferred 0.1 and

about 100 mg/kg body weight and most preferred 1.0 and about 10 mg/kg body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 7 mg to 0.7 g per day. The daily dosage can be administered as a single dosage or in divided dosages, typically between 1 and 5 dosages per day. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect for the individual patient is reached. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

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

In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

The reagents and solvents were used as purchased (from a variety of vendors), except where noted. Where applicable, the term "Celite" is used as shown in the following examples to represent the tradename CELITE® (brand of diatomaceous earth). Where applicable, chromatographic separations were performed using techniques and equipment commonly available such as, for example, by using an ISCO CombiFlash® Rf system. Where applicable, NMR spectra were obtained using techniques and equipment commonly available such as, for example, by using a Bruker Avance III^{500} spectrometer with deuterated solvents such as, for example, DMSO-d_6 or residual solvent as standard. Where applicable, TLC analysis was performed using techniques and equipment commonly available such as, for example, by using

Aldrich 254 nm glass-backed plates (60 Å, 250 μm), visualized using UV and I_2 stains. Where applicable, ESI mass spectra were obtained using techniques and equipment commonly available such as, for example, by using an ACQUITY UPLC® System, with values shown as $[M+H]^+$ or $[M-H]^-$, unless otherwise indicated. Where applicable, the structure of the product was obtained via a 2D NOESY (Nuclear Overhauser SpectroscopY) experiment.

CHEMICAL DEFINITIONS

As used herein, the term "C_{1-4}alkyl" generally refers to saturated hydrocarbon radicals having from one to four carbon atoms in a straight or branched chain configuration, including, but not limited to, methyl, ethyl, n-propyl (also referred to as propyl or propanyl), isopropyl, n-butyl (also referred to as butyl or butanyl), isobutyl, sec-butyl, tert-butyl and the like. A C_{1-4}alkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "C_{2-4}alkenyl" generally refers to partially unsaturated hydrocarbon radicals having from two to four carbon atoms in a straight or branched chain configuration and one or more carbon-carbon double bonds therein, including, but not limited to, ethenyl (also referred to as vinyl), allyl, propenyl and the like. A C_{2-4}alkenyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "C_{2-8}alkynyl" generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon triple bonds therein, including, but not limited to, ethynyl, propynyl, butynyl and the like. In certain aspects, C_{2-8}alkynyl includes, but is not limited to, C_{2-6}alkynyl, C_{2-4}alkynyl and the like. A C_{2-8}alkynyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "C_{1-4}alkoxy" generally refers to saturated hydrocarbon radicals having from one to four carbon atoms in a straight or branched chain configuration of the Formulae: -O-C_{1-4}alkyl, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like. A C_{1-4}alkoxy radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "C_{3-10}cycloalkyl" generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic hydrocarbon radical, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and the like. A C_{3-10}cycloalkyl radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "aryl" generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical, including, but not limited to, phenyl, naphthyl, anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. An aryl radical is optionally substituted with substituent species as described herein where allowed by available valences.

As used herein, the term "heteroaryl" generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with one or more heteroatoms, such as an O, S or N atom, including, but not limited to, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, 1,3-thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, indazolyl, indolizinyl, isoindolyl, benzofuranyl, benzothienyl, benzoimidazolyl, 1,3-benzothiazolyl, 1,3-benzoxazolyl, purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, 1,3-diazinyl, 1,2-diazinyl, 1,2-diazolyl, 1,4-diazanaphthalenyl, acridinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, furo[2,3-*c*]pyridinyl, 6*H*-thieno[2,3-*b*]pyrrolyl, thieno[3,2-*c*]pyridinyl, thieno[2,3-*d*]pyrimidinyl, 1*H*-pyrrolo[2,3-*b*]pyridinyl, 1*H*-pyrrolo[2,3-*c*]pyridinyl, 1*H*-pyrrolo[3,2-*b*]pyridinyl, pyrrolo[1,2-*a*]pyrazinyl, pyrrolo[1,2-*b*]pyridazinyl, pyrazolo[1,5-*a*]pyridinyl, pyrazolo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*c*]pyrimidinyl, imidazo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*b*][1,3]thiazolyl, imidazo[2,1-*b*][1,3,4]thiadiazolyl, [1,2,4]triazolo[1,5-*a*]pyridinyl, [1,2,4]triazolo[4,3-*a*]pyridinyl and the like. A heteroaryl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.

In certain aspects, the nomenclature for a heteroaryl radical may differ, such as in non-limiting examples where furanyl may also be referred to as furyl, thienyl may also be referred to

as thiophenyl, pyridinyl may also be referred to as pyridyl, benzothienyl may also be referred to as benzothiophenyl and 1,3-benzoxazolyl may also be referred to as 1,3-benzooxazolyl.

In certain other aspects, the term for a heteroaryl radical may also include other regioisomers, such as in non-limiting examples where the term pyrrolyl may also include 2*H*-pyrrolyl, 3*H*-pyrrolyl and the like, the term pyrazolyl may also include 1*H*-pyrazolyl and the like, the term imidazolyl may also include 1*H*-imidazolyl and the like, the term triazolyl may also include 1*H*-1,2,3-triazolyl and the like, the term oxadiazolyl may also include 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and the like, the term tetrazolyl may also include 1*H*-tetrazolyl, 2*H*-tetrazolyl and the like, the term indolyl may also include 1*H*-indolyl and the like, the term indazolyl may also include 1*H*-indazolyl, 2*H*-indazolyl and the like, the term benzoimidazolyl may also include 1*H*-benzoimidazolyl and the term purinyl may also include 9*H*-purinyl and the like.

As used herein, the term "heterocyclyl" generally refers to a saturated or partially unsaturated monocyclic, bicyclic or polycyclic carbon atom ring structure radical in which one or more carbon atom ring members have been replaced, where allowed by structural stability, with a heteroatom, such as an O, S or N atom, including, but not limited to, oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, pyranyl, dihydro-2*H*-pyranyl, thiopyranyl, 1,3-dioxanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,4-diazepanyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,3-dihydro-1,4-benzodioxinyl, hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, (3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, (3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-(1*H*)-yl, hexahydropyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, (3a*S*,6a*S*)-hexahydropyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, (3a*R*,6a*R*)-hexahydropyrrolo[3,4-*b*]pyrrol-(2*H*)-yl, hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, (3a*R*,6a*R*)-hexahydropyrrolo[3,4-*c*]pyrrol-(1*H*)-yl, octahydro-5*H*-pyrrolo[3,2-*c*]pyridinyl, octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4a*R*,7a*R*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl,

(7*R*,8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8a*S*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8a*R*)-hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8a*S*)-octahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (8a*R*)-octahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, hexahydropyrrolo[1,2-*a*]pyrazin-(2*H*)-one, octahydro-2*H*-pyrido[1,2-*a*]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, azaspiro[3.3]heptyl, 2,6-diazaspiro[3.3]heptyl, 2,6-diazaspiro[3.4]octyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 6,9-diazaspiro[4.5]decyl, 7-azadispiro[5.1.58.36]hexadecanyl and the like. A heterocyclyl radical is optionally substituted on a carbon or nitrogen atom ring member with substituent species as described herein where allowed by available valences.

In certain aspects, the nomenclature for a heterocyclyl radical may differ, such as in non-limiting examples where 1,3-benzodioxolyl may also be referred to as benzo[*d*][1,3]dioxolyl and 2,3-dihydro-1,4-benzodioxinyl may also be referred to as 2,3-dihydrobenzo[*b*][1,4]dioxinyl. As used herein, the term "deutero-C_{1-4}alkyl," refers to a radical of the Formulae: -C_{1-4}alkyl-deutero, wherein C_{1-4}alkyl is partially or completely substituted with one or more deuterium atoms where allowed by available valences.

For the purposes of this description, where one or more substituent variables for a compound of Formulae I-XI or a form thereof encompass functionalities incorporated into a compound of Formulae I-XI, each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.

As used herein, the terms "independently selected," or "each selected" refer to functional variables in a substituent list that may occur more than once on the structure of Formulae I-XI, the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent variable on any Formulae or structure for a compound described herein is understood to include the replacement of the generic substituent

with species substituents that are included within the particular genus, *e.g.*, aryl may be replaced with phenyl or naphthalenyl and the like, and that the resulting compound is to be included within the scope of the compounds described herein.

As used herein, the terms "each instance of" or "in each instance, when present," when used preceding a phrase such as "…C_{3-14}cycloalkyl, C_{3-14}cycloalkyl-C_{1-4}alkyl, aryl, aryl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocyclyl and heterocyclyl-C_{1-4}alkyl," are intended to refer to the C_{3-14}cycloalkyl, aryl, heteroaryl and heterocyclyl ring systems when each are present either alone or as a substituent.

As used herein, the term "optionally substituted" means optional substitution with the specified substituent variables, groups, radicals or moieties.

COMPOUND FORMS

As used herein, the term "form" means a compound of Formulae I-XI having a form selected from the group consisting of a free acid, free base, prodrug, salt, hydrate, solvate, clathrate, isotopologue, racemate, enantiomer, diastereomer, stereoisomer, polymorph and tautomer form thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is a free acid, free base or salt thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is a salt thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is an isotopologue thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is a stereoisomer, racemate, enantiomer or diastereomer thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is a tautomer thereof.

In certain aspects described herein, the form of the compound of Formulae I-XI is a pharmaceutically acceptable form.

In certain aspects described herein, the compound of Formulae I-XI or a form thereof is isolated for use.

As used herein, the term “isolated” means the physical state of a compound of Formulae I-XI or a form thereof after being isolated and/or purified from a synthetic process (*e.g.*, from a reaction mixture) or natural source or combination thereof according to an isolation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like) in sufficient purity to be characterized by standard analytical techniques described herein or well known to the skilled artisan.

As used herein, the term “protected” means that a functional group in a compound of Formulae I-XI or a form thereof is in a form modified to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T.W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York. Such functional groups include hydroxy, phenol, amino and carboxylic acid. Suitable protecting groups for hydroxy or phenol include trialkylsilyl or diarylalkylsilyl (e.g., t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, substituted benzyl, methyl, methoxymethanol, and the like. Suitable protecting groups for amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. In certain instances, the protecting group may also be a polymer resin, such as a Wang resin or a 2-chlorotrityl-chloride resin. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. It will also be appreciated by those skilled in the art, although such protected derivatives of compounds described herein may not possess pharmacological activity as such, they may be administered to a subject and thereafter metabolized in the body to form compounds described herein which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds described herein are included within the scope of the use described herein.

As used herein, the term “prodrug” means a form of an instant compound (*e.g.*, a drug precursor) that is transformed *in vivo* to yield an active compound of Formulae I-XI or a form thereof. The transformation may occur by various mechanisms (*e.g.*, by metabolic and/or nonmetabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by

T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

In one example, when a compound of Formulae I-XI or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formulae I-XI or a form thereof contains a hydroxyl functional group, a prodrug form can be prepared by replacing the hydrogen atom of the hydroxyl with another functional group such as alkyl, alkylcarbonyl or a phosphonate ester and the like. In another example, when a compound of Formulae I-XI or a form thereof contains an amine functional group, a prodrug form can be prepared by replacing one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl. Pharmaceutically acceptable prodrugs of compounds of Formulae I-XI or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters and mono-, di- or triphosphate esters or alkyl substituents, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formulae I-XI or a form thereof as a prodrug.

One or more compounds described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

As used herein, the term "solvate" means a physical association of a compound described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, "solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

The compounds of Formulae I-XI can form salts, which are intended to be included within the scope of this description. Reference to a compound of Formulae I-XI or a form thereof herein is understood to include reference to salt forms thereof, unless otherwise

indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formulae I-XI or a form thereof contains both a basic moiety, such as, without limitation an amine moiety, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein.

The term "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds described herein that are safe and effective (*i.e.*, non-toxic, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formulae I-XI may be formed, for example, by reacting a compound of Formulae I-XI or a form thereof 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.

Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds described herein. Particular aspects of acid addition salts include, and are not limited to, acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, bromide, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, iodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate salts and the like. Certain particular aspects of acid addition salts include chloride or dichloride.

Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al, Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium and zinc salts.

All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

Compounds of Formulae I-XI and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formulae I-XI or a form thereof as described herein.

The compounds of Formulae I-XI or a form thereof may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. The present description is intended to include all stereoisomeric forms of the compounds of Formulae I-XI as well as mixtures thereof, including racemic mixtures.

The compounds described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one particular aspect, the compounds described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another particular aspect, the compounds described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) isomer, as defined by *IUPAC* Nomenclature Recommendations.

As used herein, the term "substantially pure" refers to compounds consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

In one aspect of the description, a compound of Formulae I-XI or a form thereof is a substantially pure (*S*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount

greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

In one aspect of the description, a compound of Formulae I-XI or a form thereof is a substantially pure (*R*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

As used herein, a "racemate" is any mixture of isometric forms that are not "enantiomerically pure", including mixtures such as, without limitation, in a ratio of about 50/50, about 60/40, about 70/30, or about 80/20.

In addition, the present description embraces all geometric and positional isomers. For example, if a compound of Formulae I-XI or a form thereof incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the description. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by use of chiral HPLC column or other chromatographic methods known to those skilled in the art. Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formulae I-XI may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this description.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this description, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds described

herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described supra.

The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or isotopologues of the instant compounds.

The term "isotopologue" refers to isotopically-enriched compounds described herein which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{35}Cl and ^{36}Cl, respectively, each of which are also within the scope of this description.

Certain isotopically-enriched compounds described herein (*e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Polymorphic crystalline and amorphous forms of the compounds of Formulae I-XI and of the salts, solvates, hydrates, esters and prodrugs of the compounds of Formulae I-XI are further intended to be included in the present description.

COMPOUND USES

In accordance with the intended scope of the present description, aspects of the present description include compounds that have been identified and have been demonstrated to be useful in selectively preventing, treating or ameliorating any disease that is mediated by NLRP3 and have been provided for use for preventing, treating or ameliorating any disease that is mediated by NLRP3.

An aspect of the present description includes a method for preventing, treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising,

administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

An aspect of the present description includes a method for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

An aspect of the present description includes a method for preventing any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

An aspect of the present description includes a method for treating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

An aspect of the present description includes a method for ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formulae I-XI or a form thereof.

Another aspect of the present description includes a method for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of a compound salt of Formulae I-XI or a form thereof.

An aspect of the present description includes a method for use of a compound of Formulae I-XI or a form or composition thereof for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formulae I-XI or a form or composition thereof.

Another aspect of the present description includes a method for use of a compound salt of Formulae I-XI or a form or composition thereof for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formulae I-XI or a form thereof.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formulae I-XI or a form thereof.

Another aspect of the present description includes a use for a compound salt of Formulae I-XI or a form thereof for treating or ameliorating any disease that is mediated by NLRP3 in a

subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formulae I-XI or a form thereof.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in the manufacture of a medicament for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.

Another aspect of the present description includes a use for a compound salt of Formulae I-XI or a form thereof in the manufacture of a medicament for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the medicament.

An aspect of the present description includes in vitro or in vivo use of the compound of Formulae I-XI or a form thereof having activity toward any disease that is mediated by NLRP3. An aspect of the present description includes a use of the compound of Formulae I-XI or a form thereof in a combination therapy to provide additive or synergistic activity, thus enabling the development of a combination product for treating or ameliorating any disease that is mediated by NLRP3.

Another aspect of the present description includes a combination therapy comprising compounds described herein in combination with one or more known drugs or one or more known therapies may be used to treat any disease that is mediated by NLRP3 regardless of whether any disease that is mediated by NLRP3 is responsive to the known drug.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formulae I-XI or a form thereof in combination with an effective amount of the one or more agents.

Another aspect of the present description includes a use for a compound salt of Formulae I-XI or a form thereof in a combination product with one or more therapeutic agents for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound salt of Formulae I-XI or a form thereof in combination with an effective amount of the one or more agents.

In an aspect of a use or method provided herein, compounds of Formulae I-XI or a form thereof used in combination with one or more additional agents can be administered to a subject or contacted with a subject or patient cell(s) prior to, concurrently with, or subsequent to administering to the subject or patient or contacting the cell with an additional agent(s). A compound(s) of Formulae I-XI or a form thereof and an additional agent(s) can be administered to a subject or contacted with a cell in single composition or different compositions. In a specific aspect, a compound(s) of Formulae I-XI or a form thereof is used in combination with gene therapy to inhibit NLRP3 expression (using, *e.g.*, viral delivery vectors) or the administration of another small molecule Nlrp3 inhibitor. In another specific aspect, a compound(s) of Formulae I-XI or a form thereof are used in combination with cell replacement using differentiated non-mutant NLRP3 stem cells. In another specific aspect, a compound(s) of Formulae I-XI or a form thereof are used in combination with cell replacement using differentiated NLRP3 stem cells.

In one aspect, provided herein is the use of compounds of Formulae I-XI or a form thereof in combination with supportive standard of care therapies, including palliative care.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in the preparation of a kit for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, the compound of Formulae I-XI or a form thereof and instructions for administering an effective amount of the compound of Formulae I-XI or a form thereof.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in the preparation of a kit for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, the compound of Formulae I-XI or a form thereof and instructions for administering an effective amount of the compound of Formulae I-XI or a form thereof; and optionally, for administering to the subject an effective amount of the compound of Formulae I-XI or a form thereof in a combination product with an effective amount of one or more therapeutic agents.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in the preparation of a kit for treating or ameliorating any disease that is mediated by NLRP3 in a subject in need thereof comprising, the compound of Formulae I-XI or a form thereof and instructions for administering an effective amount of the compound of Formulae I-XI or a form thereof; and optionally, for administering to the subject an effective amount of the

compound of Formulae I-XI or a form thereof in a combination product with an effective amount of the one or more therapeutic agents; and optionally, for administering to the subject an effective amount of the compound of Formulae I-XI or a form thereof in a combination product with an effective amount of the one or more therapeutic agents in a combination therapy with a standard of care supportive therapy, wherein the standard of care supportive therapy is palliative care.

In one respect, for each of such aspects, the subject is treatment naive. In another respect, for each of such aspects, the subject is not treatment naive.

As used herein, the term “preventing” refers to keeping a disease, disorder or condition from occurring in a subject that may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having the disease, disorder and/or condition.

As used herein, the term “treating” refers to inhibiting the progression of a disease, disorder or condition in a subject already exhibiting the symptoms of the disease, disorder and/or condition, *i.e.*, arresting the development of a disease, disorder and/or condition that has already affected the subject.

As used herein, the term “ameliorating” refers to relieving the symptoms of a disease, disorder or condition in a subject already exhibiting the symptoms of the disease, disorder and/or condition, *i.e.*, causing regression of the disease, disorder and/or condition that has already affected the subject.

As used herein, the term “subject” refers to an animal or any living organism having sensation and the power of voluntary movement, and which requires oxygen and organic food. Nonlimiting examples include members of the human, primate, equine, porcine, bovine, murine, rattus, canine and feline specie. In certain aspects, the subject is a mammal or a warm-blooded vertebrate animal. In other aspects, the subject is a human. As used herein, the term “patient” may be used interchangeably with “subject” and “human”.

As used herein, the terms “effective amount” or "therapeutically effective amount" mean an amount of compound of Formulae I-XI or a form, composition or medicament thereof that achieves a target plasma concentration that is effective in treating or ameliorating any disease that is mediated by NLRP3 as described herein and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect in a subject in need thereof. In one aspect, the

effective amount may be the amount required to treat any disease that is mediated by NLRP3 in a subject or patient, more specifically, in a human.

In another aspect, the concentration-biological effect relationships observed with regard to a compound of Formulae I-XI or a form thereof indicate a target plasma concentration ranging from approximately 0.001 μg/mL to approximately 50 μg/mL, from approximately 0.01 μg/mL to approximately 20 μg/mL, from approximately 0.05 μg/mL to approximately 10 μg/mL, or from approximately 0.1 μg/mL to approximately 5 μg/mL. To achieve such plasma concentrations, the compounds described herein may be administered at doses that vary, such as, for example, without limitation, from 1.0 ng to 10,000 mg.

In one aspect, the dose administered to achieve an effective target plasma concentration may be administered based upon subject or patient specific factors, wherein the doses administered on a weight basis may be in the range of from about 0.001 mg/kg/day to about 3500 mg/kg/day, or about 0.001 mg/kg/day to about 3000 mg/kg/day, or about 0.001 mg/kg/day to about 2500 mg/kg/day, or about 0.001 mg/kg/day to about 2000 mg/kg/day, or about 0.001 mg/kg/day to about 1500 mg/kg/day, or about 0.001 mg/kg/day to about 1000 mg/kg/day, or about 0.001 mg/kg/day to about 500 mg/kg/day, or about 0.001 mg/kg/day to about 250 mg/kg/day, or about 0.001 mg/kg/day to about 200 mg/kg/day, or about 0.001 mg/kg/day to about 150 mg/kg/day, or about 0.001 mg/kg/day to about 100 mg/kg/day, or about 0.001 mg/kg/day to about 75 mg/kg/day, or about 0.001 mg/kg/day to about 50 mg/kg/day, or about 0.001 mg/kg/day to about 25 mg/kg/day, or about 0.001 mg/kg/day to about 10 mg/kg/day, or about 0.001 mg/kg/day to about 5 mg/kg/day, or about 0.001 mg/kg/day to about 1 mg/kg/day, or about 0.001 mg/kg/day to about 0.5 mg/kg/day, or about 0.001 mg/kg/day to about 0.1 mg/kg/day, or from about 0.01 mg/kg/day to about 3500 mg/kg/day, or about 0.01 mg/kg/day to about 3000 mg/kg/day, or about 0.01 mg/kg/day to about 2500 mg/kg/day, or about 0.01 mg/kg/day to about 2000 mg/kg/day, or about 0.01 mg/kg/day to about 1500 mg/kg/day, or about 0.01 mg/kg/day to about 1000 mg/kg/day, or about 0.01 mg/kg/day to about 500 mg/kg/day, or about 0.01 mg/kg/day to about 250 mg/kg/day, or about 0.01 mg/kg/day to about 200 mg/kg/day, or about 0.01 mg/kg/day to about 150 mg/kg/day, or about 0.01 mg/kg/day to about 100 mg/kg/day, or about 0.01 mg/kg/day to about 75 mg/kg/day, or about 0.01 mg/kg/day to about 50 mg/kg/day, or about 0.01 mg/kg/day to about 25 mg/kg/day, or about 0.01 mg/kg/day to about 10 mg/kg/day, or about 0.01 mg/kg/day to about 5 mg/kg/day, or about 0.01 mg/kg/day to about 1

mg/kg/day, or about 0.01 mg/kg/day to about 0.5 mg/kg/day, or about 0.01 mg/kg/day to about 0.1 mg/kg/day, or from about 0.1 mg/kg/day to about 3500 mg/kg/day, or about 0.1 mg/kg/day to about 3000 mg/kg/day, or about 0.1 mg/kg/day to about 2500 mg/kg/day, or about 0.1 mg/kg/day to about 2000 mg/kg/day, or about 0.1 mg/kg/day to about 1500 mg/kg/day, or about 0.1 mg/kg/day to about 1000 mg/kg/day, or about 0.1 mg/kg/day to about 500 mg/kg/day, or about 0.1 mg/kg/day to about 250 mg/kg/day, or about 0.1 mg/kg/day to about 200 mg/kg/day, or about 0.1 mg/kg/day to about 150 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day, or about 0.1 mg/kg/day to about 75 mg/kg/day, or about 0.1 mg/kg/day to about 50 mg/kg/day, or about 0.1 mg/kg/day to about 25 mg/kg/day, or about 0.1 mg/kg/day to about 10 mg/kg/day, or about 0.1 mg/kg/day to about 5 mg/kg/day, or about 0.1 mg/kg/day to about 1 mg/kg/day, or about 0.1 mg/kg/day to about 0.5 mg/kg/day.

Effective amounts for a given subject may be determined by routine experimentation that is within the skill and judgment of a clinician or a practitioner skilled in the art in light of factors related to the subject. Dosage and administration may be adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include genetic screening, severity of the disease state, status of disease progression, general health of the subject, ethnicity, age, weight, gender, diet, time of day and frequency of administration, drug combination(s), reaction sensitivities, experience with other therapies, and tolerance/response to therapy.

The dose administered to achieve an effective target plasma concentration may be orally administered once (once in approximately a 24 hour period; i.e., "q.d."), twice (once in approximately a 12 hour period; i.e., "b.i.d." or "q.12h"), thrice (once in approximately an 8 hour period; i.e., "t.i.d." or "q.8h"), or four times (once in approximately a 6 hour period; i.e., "q.d.s.", "q.i.d." or "q.6h") daily.

In certain aspects, the dose administered to achieve an effective target plasma concentration may also be administered in a single, divided, or continuous dose for a patient or subject having a weight in a range of between about 40 to about 200 kg (which dose may be adjusted for patients or subjects above or below this range, particularly children under 40 kg). The typical adult subject is expected to have a median weight in a range of about 70 kg. Long-acting pharmaceutical compositions may be administered every 2, 3 or 4 days, once every week,

or once every two weeks depending on half-life and clearance rate of the particular Formulaetion.

The compounds and compositions described herein may be administered to the subject via any drug delivery route known in the art. Nonlimiting examples include oral, ocular, rectal, buccal, topical, nasal, sublingual, transdermal, subcutaneous, intramuscular, intraveneous (bolus and infusion), intracerebral, and pulmonary routes of administration.

In another aspect, the dose administered may be adjusted based upon a dosage form described herein Formulaeted for delivery at about 0.02, 0.025, 0.03, 0.05, 0.06, 0.075, 0.08, 0.09, 0.10, 0.20, 0.25, 0.30, 0.50, 0.60, 0.75, 0.80, 0.90, 1.0, 1.10, 1.20, 1.25, 1.50, 1.75, 2.0, 3.0, 5.0, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 400, 500, 1000, 1500, 2000, 2500, 3000 or 4000 mg/day.

For any compound, the effective amount can be estimated initially either in cell culture assays or in relevant animal models, such as a mouse, guinea pig, chimpanzee, marmoset or tamarin animal model. Relevant animal models may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is therapeutic index, and can be expressed as the ratio, LD_{50}/ED_{50}. In certain aspects, the effective amount is such that a large therapeutic index is achieved. In further particular aspects, the dosage is within a range of circulating concentrations that include an ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

In one aspect, provided herein are methods for modulating the amount of NLRP3, comprising contacting a human cell with a compound of Formulae I-XI or a form thereof. In a specific aspect, provided herein are methods for modulating the amount of NLRP3, comprising contacting a human cell with a compound of Formulae I-XI or a form thereof that modulates the expression of NLRP3. The human cell can be contacted with a compound of Formulae I-XI or a form thereof *in vitro*, or *in vivo*, *e.g.*, in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with any disease that is modulated by NLRP3. In another specific aspect, the human cell

is from or in a human with any disease that is modulated by NLRP3, resulting in a loss of NLRP# expression and/or function. In another aspect, the human cell is from a human with H any disease that is modulated by NLRP3. In another aspect, the human cell is in a human with any disease that is modulated by NLRP3. In one aspect, the compound is a form of a compound of Formulae I-XI.

In a specific aspect, provided herein is a method for enhancing the inhibition of mutant NLRP# transcribed from the NLRP3 gene, comprising contacting a human cell with a compound of Formulae I-XI or a form thereof. The human cell can be contacted with a compound of Formulae I-XI or a form thereof *in vitro*, or *in vivo*, *e.g.*, in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with any disease that is modulated by NLRP3. In another specific aspect, the human cell is from or in a human with HD, caused by a CAG repeat in the NLRP3 gene, resulting in a loss of wild-type "normal" NLRP# expression and/or function. In another aspect, the human cell is from a human with any disease that is modulated by NLRP3. In another aspect, the human cell is in a human with any disease that is modulated by NLRP3. In one aspect, the compound is a form of the compound of Formulae I-XI.

In another aspect, provided herein is a method for modulating the inhibition of mutant NLRP3 transcribed from the NLRP3 gene, comprising administering to a non-human animal model for any disease that is modulated by NLRP3 a compound of Formulae I-XI or a form thereof. In a specific aspect, provided herein is a method for modulating the inhibition of mutant NLRP3transcribed from the HNLRP3 gene, comprising administering to a non-human animal model for any disease that is modulated by NLRP3 a compound of Formulae I-XI or a form thereof. In a specific aspect, the compound is a form of the compound of Formulae I-XI.

In another aspect, provided herein is a method for decreasing the amount of mutant NLRP3, comprising contacting a human cell with a compound of Formulae I-XI or a form thereof. In a specific aspect, provided herein is a method for decreasing the amount of mutant NLRP3, comprising contacting a human cell with a compound of Formulae I-XI that inhibits the transcription of mutant *NLRP3* from the NLRP3 gene. In another specific aspect, provided herein is a method for decreasing the amount of NLRP3, comprising contacting a human cell with a compound of Formulae I-XI that inhibits the expression of mutant NLRP3 transcribed from the NLRP3 gene. The human cell can be contacted with a compound of Formulae I-XI or a

form thereof *in vitro*, or *in vivo*, *e.g.*, in a non-human animal or in a human. In a specific aspect, the human cell is from or in a human. In another specific aspect, the human cell is from or in a human with any disease that is modulated by NLRP3. In another specific aspect, the human cell is from or in a human with any disease that is modulated by NLRP3. In another aspect, the human cell is from a human with any disease that is modulated by NLRP3. In another aspect, the human cell is in a human with any disease that is modulated by NLRP3. In one aspect, the compound is a form of the compound of Formulae I-XI.

In certain aspects, treating or ameliorating any disease that is modulated by NLRP3 with a compound of Formulae I-XI or a form thereof (alone or in combination with an additional agent) has a therapeutic effect and/or beneficial effect. In a specific aspect, treating any disease that is modulated by NLRP3 with a compound of Formulae I-XI or a form thereof (alone or in combination with an additional agent) results in one, two or more of the following effects: (i) reduces or ameliorates the severity of any disease that is modulated by NLRP3; (ii) delays onset of any disease that is modulated by NLRP3; (iii) inhibits the progression of any disease that is modulated by NLRP3; (iv) reduces hospitalization of a subject; (v) reduces hospitalization length for a subject; (vi) increases the survival of a subject; (vii) improves the quality of life for a subject; (viii) reduces the number of symptoms associated with any disease that is modulated by NLRP3; (ix) reduces or ameliorates the severity of a symptom(s) associated with any disease that is modulated by NLRP3; (x) reduces the duration of a symptom associated with any disease that is modulated by NLRP3; (xi) prevents the recurrence of a symptom associated with any disease that is modulated by NLRP3; (xii) inhibits the development or onset of a symptom of any disease that is modulated by NLRP3; and/or (xiii) inhibits of the progression of a symptom associated with any disease that is modulated by NLRP3.

METABOLITES

Another aspect included within the scope of the present description are the use of *in vivo* metabolic products of the compounds described herein. Such products may result, for example, from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the description includes the use of compounds produced by a process comprising contacting a compound

described herein with a mammalian tissue or a mammal for a period of time sufficient to yield a metabolic product thereof.

Such products typically are identified by preparing a radio-labeled isotopologue (*e.g.*, ^{14}C or ^{3}H) of a compound described herein, administering the radio-labeled compound in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to a mammal such as a rat, mouse, guinea pig, dog, monkey or human, allowing sufficient time for metabolism to occur (typically about 30 seconds to about 30 hours), and identifying the metabolic conversion products from urine, bile, blood or other biological samples. The conversion products are easily isolated since they are "radiolabeled" by virtue of being isotopically-enriched (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites may be done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds described herein even if they possess no biological activity of their own.

PHARMACEUTICAL COMPOSITIONS

In accordance with the intended scope of the present description, aspects of the present description include compounds that have been identified and have been demonstrated to be useful in selectively preventing, treating or ameliorating any disease that is modulated by NLRP3 and have been provided for use as one or more pharmaceutical compositions for preventing, treating or ameliorating any disease that is modulated by NLRP3.

An aspect of the present description includes a use for a compound of Formulae I-XI or a form thereof in the preparation of a pharmaceutical composition for treating or ameliorating any disease that is modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formulae I-XI or a form thereof in admixture with one or more pharmaceutically acceptable excipients.

An aspect of the present description includes a use for a pharmaceutical composition of the compound of Formulae I-XI or a form thereof in the preparation of a kit for treating or ameliorating any disease that is modulated by NLRP3 in a subject in need thereof comprising,

the pharmaceutical composition of the compound of Formulae I-XI or a form thereof and instructions for administering the pharmaceutical composition.

As used herein, the term "composition" means a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical composition may be formulated to achieve a physiologically compatible pH, ranging from about pH 3 to about pH 11. In certain aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 3 to about pH 7. In other aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 5 to about pH 8.

The term "pharmaceutically acceptable excipient" refers to an excipient for administration of a pharmaceutical agent, such as the compounds described herein. The term refers to any pharmaceutical excipient that may be administered without undue toxicity. Pharmaceutically acceptable excipients may be determined in part by the particular composition being administered, as well as by the particular mode of administration and/or dosage form. Nonlimiting examples of pharmaceutically acceptable excipients include carriers, solvents, stabilizers, adjuvants, diluents, *etc.* Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions for the instant compounds described herein (*see, e.g.*, Remington's Pharmaceutical Sciences).

Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive antibodies. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose (*e.g.*, hydroxypropylmethylcellulose, also known as HPMC), stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

The pharmaceutical compositions described herein may be formulated in any form suitable for the intended use described herein. Suitable formulations for oral administration include solids, liquid solutions, emulsions and suspensions, while suitable inhalable formulations for pulmonary administration include liquids and powders. Alternative formulations include

syrups, creams, ointments, tablets, and lyophilized solids which can be reconstituted with a physiologically compatible solvent prior to administration.

When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents, and preserving agents, in order to provide a palatable preparation.

Pharmaceutically acceptable excipients suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid, or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin, or olive oil.

In other aspects, pharmaceutical compositions described herein may be formulated as suspensions comprising a compound of Formulae I-XI, or a form thereof in admixture with one or more pharmaceutically acceptable excipients suitable for the manufacture of a suspension. In yet other aspects, pharmaceutical compositions described herein may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of one or more excipients.

Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium

alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

Additionally, the pharmaceutical compositions described herein may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. Such emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propanediol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The compounds described herein may be substantially insoluble in water and sparingly soluble in most pharmaceutically acceptable protic solvents and vegetable oils, but generally soluble in medium-chain fatty acids (*e.g.*, caprylic and capric acids) or triglycerides and in propylene glycol esters of medium-chain fatty acids. Thus, contemplated in the description are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (*e.g.*, increase solubility, bioactivity, palatability, decrease adverse reactions, *etc.*), for example by esterification, glycosylation, PEGylation, etc.

In certain aspects, the compound described herein is formulated for oral administration in a lipid-based composition suitable for low solubility compounds. Lipid-based formulations can generally enhance the oral bioavailability of such compounds. As such, pharmaceutical compositions described herein may comprise a effective amount of a compound of Formulae I-XI or a form thereof, together with at least one pharmaceutically acceptable excipient selected from medium chain fatty acids or propylene glycol esters thereof (*e.g.*, propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants, such as polysorbate 20 or 80 (also referred to as Tween® 20 or Tween® 80, respectively) or polyoxyl 40 hydrogenated castor oil.

In other aspects, the bioavailability of low solubility compounds may be enhanced using particle size optimization techniques including the preparation of nanoparticles or nanosuspensions using techniques known to those skilled in the art. The compound forms present in such preparations include amorphous, partially amorphous, partially crystalline or crystalline forms.

In alternative aspects, the pharmaceutical composition may further comprise one or more aqueous solubility enhancer(s), such as a cyclodextrin. Nonlimiting examples of cyclodextrin include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin, and hydroxypropyl-β-cyclodextrin (HPBC). In certain aspects, the pharmaceutical composition further comprises HPBC in a range of from about 0.1% to about 20%, from about 1% to about 15%, or from about 2.5% to about 10%. The amount of solubility enhancer employed may depend on the amount of the compound in the composition.

EXPERIMENTAL

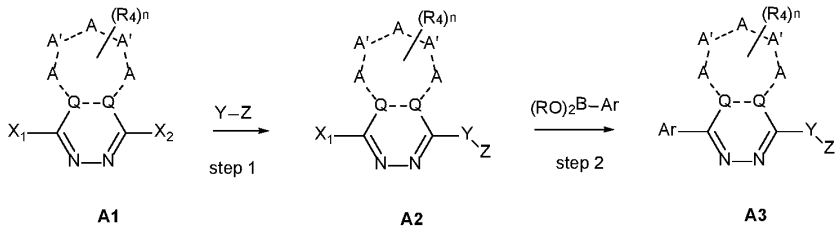
PREPARATION OF COMPOUNDS

GENERAL SYNTHETIC METHODS

As disclosed herein, general methods for preparing the compounds of Formulae I-XI or a form thereof as described herein can be prepared using the methods summarized in Schemes A-I by the suitable selection of reagents with appropriate substitution, solvents, temperatures, pressures, and other reaction conditions readily selected by one of ordinary skilled in the art. Many of the starting materials are commercially available or, when not available, can be prepared via standard, well-known synthetic methodology or using the routes described below using techniques known to those skilled in the art. The synthetic schemes provided herein comprise multiple reaction steps, each of which is intended to stand on its own and can be carried out with or without any preceding or succeeding step(s). In other words, each of the individual reaction steps of the synthetic schemes provided herein in isolation is contemplated.

Depending on the nature of the groups Ar, A, A', Q, X_1, X_2, Y, Z, R_1, R_2 and R_{4b}, depicted in the schemes below, the final compounds or their precursors may be further elaborated using the standard, well-known synthetic methods such as SNAr displacement reaction, metal catalyzed coupling reactions like Suzuki coupling, Negishi coupling and Buchwald coupling, reductive amination, etc. to afford the compounds of the general Formulae I-XI.

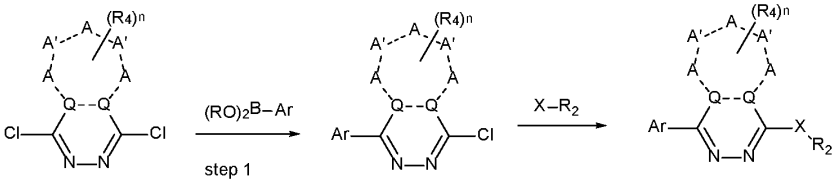
Scheme A:



A1 A2 A3

Compound **A1** (where X_1 and X_2 are independently bromine, chlorine and the like) is converted to Compound **A2** by a nucleophilic substitution with either an appropriate amine in the presence of a suitable base (such as DIEPA and the like) in a suitable solvent (such as NMP and the like) or with an appropriate alcohol in the presence of a suitable base (such as NaH and the like) in a suitable solvent (such as anhydrous THF and the like). Compound **A2** is converted to Compound **A3** by a Suzuki coupling with an aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $Pd(dppf)Cl_2$ and the like) and base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like).

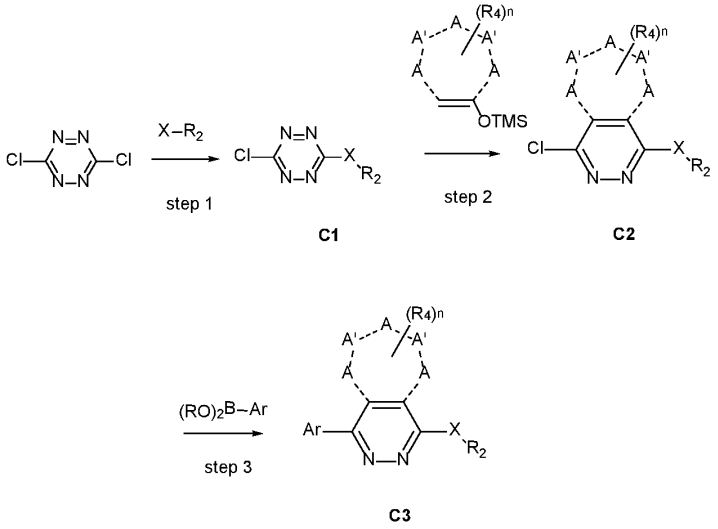
Scheme B:



B1 B2 B3

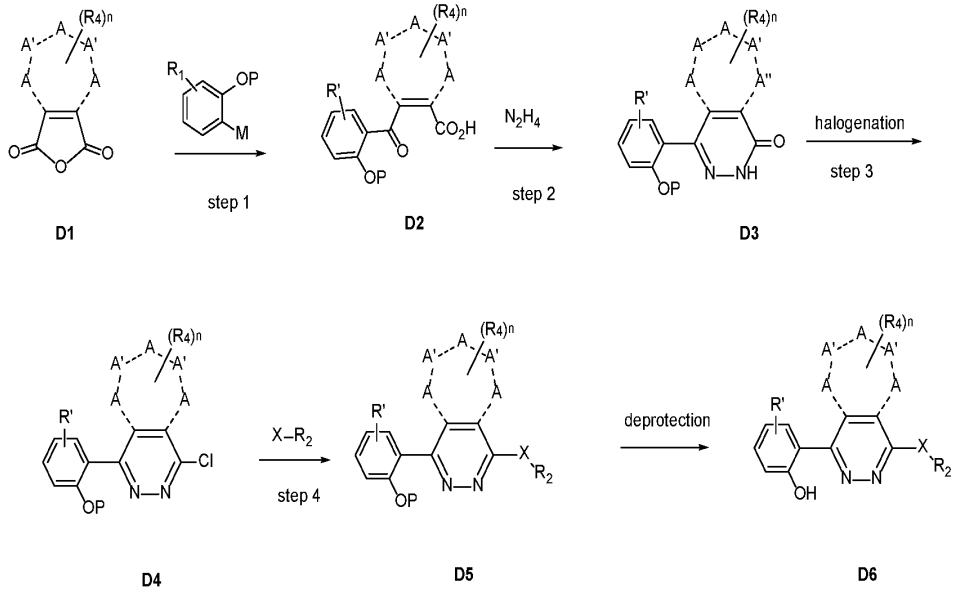
Compound **B1** is converted to Compound **B2** by a Suzuki coupling with an aryl- or heteroaryl-boronic acid (or pinacol boronic ester) in the presence of a catalyst (such as $Pd(dppf)Cl_2$ and the like) and base (such as aqueous K_2CO_3 and the like) in a suitable solvent (such as 1,4-dioxane and the like). Compound **B2** is converted to Compound **B3** by a Buchwald-Hartwig coupling with an appropriate amine in the present of a catalyst (such as $Pd_2(dba)_3$ and the like), a ligand (such as RuPhos and the like) and a base (such as NaO^tBu and the like) in a suitable solvent (such as PhMe and the like).

Scheme C:



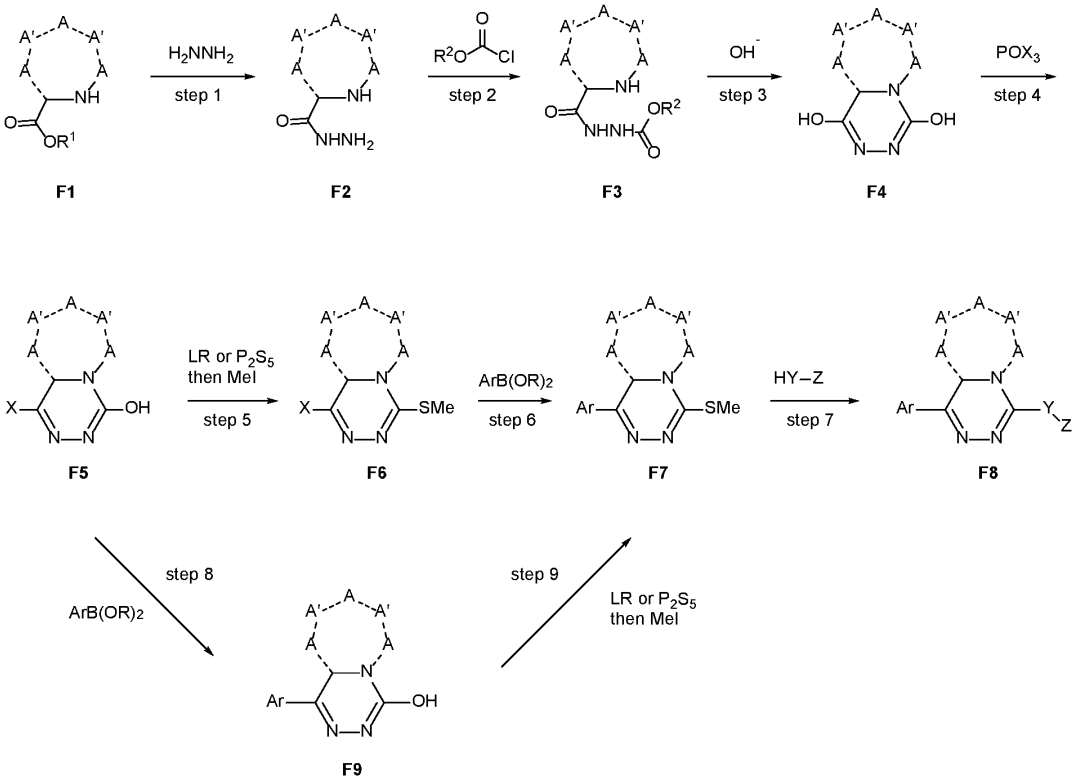
Compound **C1** was prepared from 1,2,4,5-tetrazines with an appropriate amine in the presence of a suitable base (such as DIEPA and the like) in a suitable solvent (such as DCM and the like). **Compound C1** was converted to **Compound C2** by inverse electron demand Diels-Alder reaction with an appropriate enol ethers or enamine in a suitable solvent (such as PhMe and the like). Following conditions described in Scheme A - step 2, compound **C2** was converted to compound **C3**.

Scheme D:



Compound **D1** is converted to Compound **D2** (where P is a protecting group such as Me and the like) by reacting with an appropriate organometallic compound (such as Grignard reagent and the like) in a suitable solvent (such as THF and the like). Compound **D2** is converted to Compound **D3** by condensation/cyclization sequence in the present of hydrazine in a suitable solvent (such as EtOH and the like). Compound **D3** is converted to Compound **D4** by treatment with a dehydrative halogenating agent (such as $POCl_3$ and the like). Compound **D4** is converted to Compound **D5** by a Buchwald-Hartwig coupling with an appropriate amine in the present of a catalyst (such as $Pd_2(dba)_3$ and the like), a ligand (such as RuPhos and the like) and a base (such as NaO^tBu and the like) in a suitable solvent (such as PhMe and the like). Compound **D5** is converted to Compound **D6** upon treatment with conditions appropriate to removal of the protection groups (such as BBr_3 in DCM for a Me protection group in suitable solvent (such as DCM and the like).

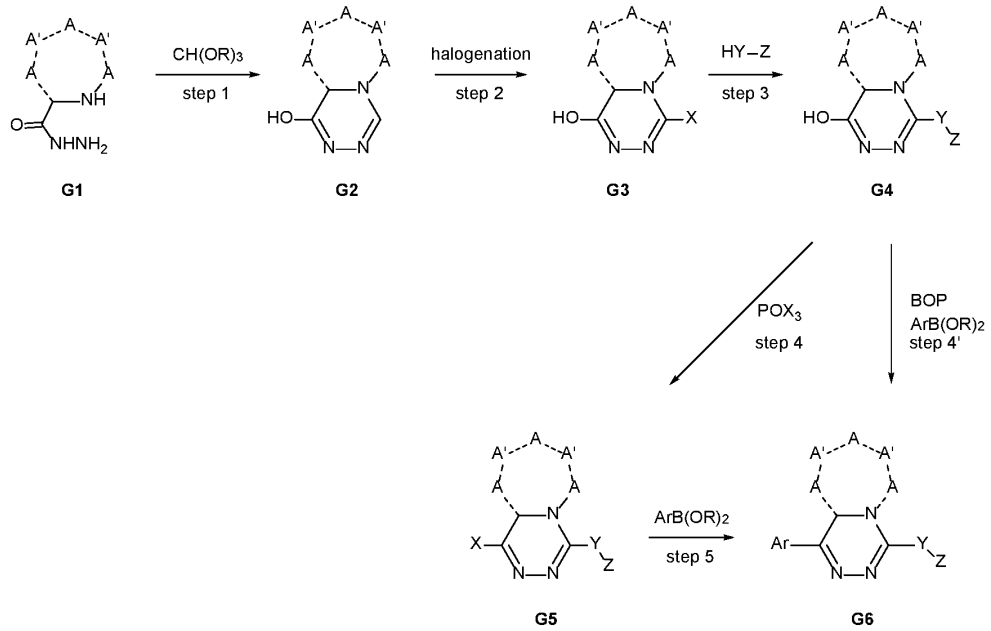
Scheme F:



Compound **F1** is converted to compound **F2** by reacting with hydrazine in a suitable solvent (such as EtOH and the like). Reaction of **F2** with chloroformate in the presence of a base (such as DIPEA and the like) in a suitable solvent (such as DCM and the like) provides **F3**, which is cyclized to **F4** by treating with a base (such as KOH and the like) in a suitable solvent (such as EtOH and the like) at an elevated temperature (such as 80°C and the like). Compound **F4** is converted to compound **F5** by treating with POX_3 (X= Cl or Br) with or without a base (such as DIPEA and the like). Treatment of **F5** with a thionating reagent such as Lawesson's Reagent (LR) or P_2S_5 at an appropriate temperature such as 100°C, followed by alkylation with MeI provides **F6**. Compound **F6** is converted to **F7** by Suzuki coupling with an aryl or hetero boronic acid or borate in the presence of a suitable catalyst (such as $PdCl_2$dppf and the like) and a base (such as K_2CO_3 and the like) in a suitable solvent (such as dioxane and the like). Alternatively, compound **F5** is converted to compound **F7** by a Suzuki coupling first to give compound **F9**, followed by thionation with LR or P_2S_5 and subsequent alkylation with MeI.

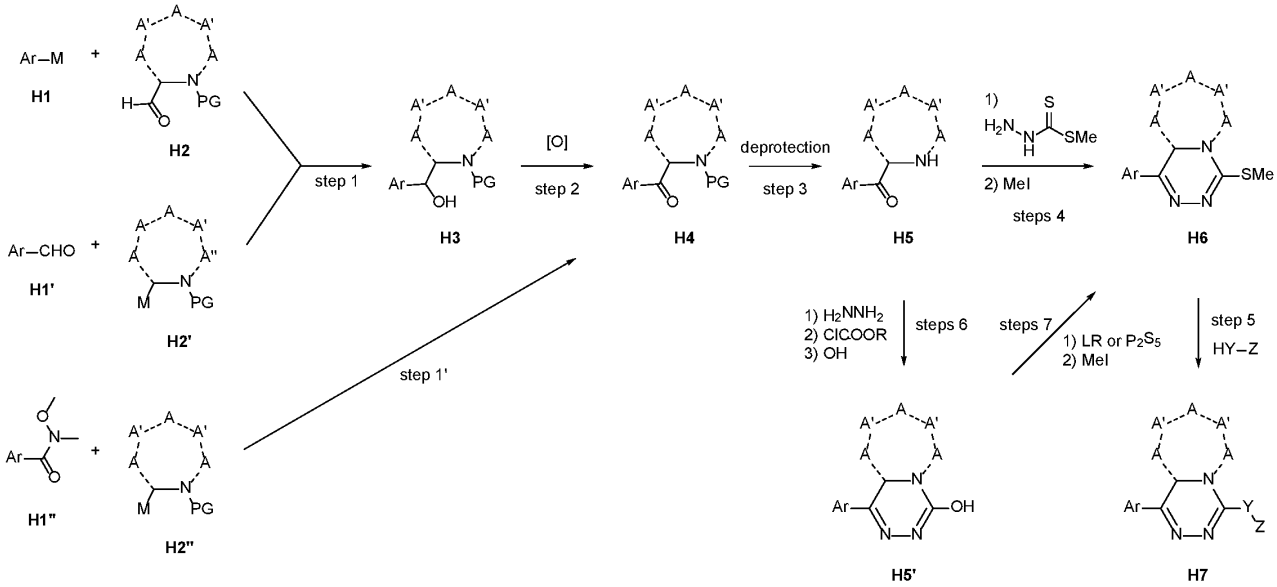
SNAr reaction of **F7** with a nucleophile in a suitable solvent (such as DMSO and the like) at an elevated temperature (such as 130°C and the like) provides **F8**.

Scheme G:



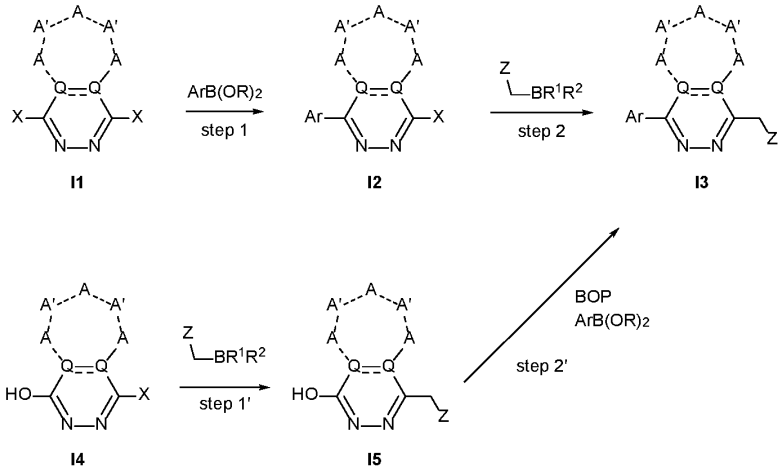
Compound **G1**, prepared according to step 1 in scheme F, is converted to compound **G2** by reacting with tri-alkoxy orthoformate in a suitable solvent (such as EtOH and the like) at an elevated temperature (such as 100°C and the like). Reaction of **G2** with a halogenation reagent (such as NBS and the like) in a suitable solvent (such as DMF and the like) provides **G3**, which is reacted with a nucleophile to give the compound **G4**. Compound **G4** is converted to compound **G5** by treating with POX_3 (X= Cl or Br) with or without a base (such as DIPEA and the like) at an elevated temperature (such as 100°C and the like). Suzuki coupling of compound **G5** with an aryl or heteroaryl boronic acid or borate in the presence of a suitable catalyst (such as $PdCl_2dppf$ and the like) and a base (such as K_2CO_3 and the like) in a suitable solvent (such as dioxane and the like) provides **G6**. Alternatively, compound **G4** can be converted to compound **G6** directly by a BOP-medicated Suzuki coupling.

Scheme H:



Reaction of an organometallic compound with an aldehyde, either **H1** with **H2**, or **H1'** with **H2'**, affords the alcohol **H3**. Compound **H3** is converted to **H4** by treating with an oxidant (such as MnO_2 and the like) in a suitable solvent (such as DCM and the like). Alternatively, reaction of compounds **H1"** with **H2"** yields **H4** directly. Deprotection of compound **H4** provides compound **H5**. Reaction of compound **H5** with methyl hydrazinecarbodithioate in a suitable solvent (such as EtOH and the like) at an elevated temperature (such as 80°C and the like) followed by alkylation with MeI in the presence of a base (such as K_2CO_3 and the like) provides compound **H6**. Alternatively, compound **H5** is converted to compound **H5'** by reacting with hydrazine in a suitable solvent (such as EtOH and the like), followed by reaction with chloroformate in the presence of a base (such as DIPEA and the like) in a suitable solvent (such as DCM and the like) and cyclization by treating with a base (such as KOH and the like) in a suitable solvent (such as EtOH and the like) at an elevated temperature (such as 80°C and the like). SNAr reaction of **H6** with a nucleophile in a suitable solvent (such as DMSO and the like) at an elevated temperature (such as 130°C and the like) provides **H7**.

Scheme I:



Compound **I1** is converted to compound **I3** by two coupling reactions with boronic acids or borates in the presence of a suitable catalyst (such as $PdCl_2dppf$ and the like) and a base (such as K_2CO_3 and the like) in a suitable solvent (such as dioxane and the like). Alternatively, compound **I4** is converted to compound **I5** by coupling with a boronic acid or borate, which is further converted to compound **I3** by a BOP-mediated Suzuki coupling with an aryl or heteroaryl boronic acid or borate.

SYNTHETIC EXAMPLES

To describe in more detail and assist in understanding, the following non-limiting examples are offered to more fully illustrate the scope of compounds described herein and are not to be construed as specifically limiting the scope thereof. Such variations of the compounds described herein that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the compounds as described herein and hereinafter claimed. These examples illustrate the preparation of certain compounds. Those of skill in the art will understand that the techniques described in these examples represent techniques, as described by those of ordinary skill in the art, that function well in synthetic practice, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those of skill in the art should, in light of the present

disclosure, appreciate that many changes can be made in the specific methods that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the present description.

Other than in the following examples of the embodied compounds, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term "about". Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term "about" in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and rounding techniques used by those of skill in the art.

While the numerical ranges and parameters setting forth the broad scope of the present description are approximations, the numerical values set forth in the examples set forth below are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

COMPOUND EXAMPLES

As used above, and throughout the present description, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

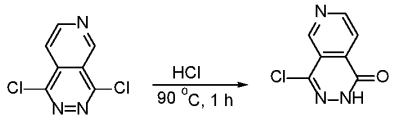
Abbreviation	**Meaning**
9-BBN	9-borabicyclo[3.3.1]nonane
AcOH or HOAc	acetic acid
ACN or MeCN	acetonitrile
Ar	argon gas
aq.	aqueous
BBr_3	boron tribromide

Abbreviation	Meaning
BippyPhos	5-(Di-tert-butylphosphino)-1′, 3′, 5′-triphenyl-1′H-[1,4′]bipyrazole
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Br_2	bromine
*n*BuLi	n-butyl lithium
$CaCO_3$	calcium carbonate
Cbz-Cl	benzyl chloroformate or benzyl chlorocarbonate or Z-chloride
$CDCl_3$	deuterated chloroform or chloroform-d
Celite	diatomaceous earth
CH_2Cl_2 or DCM	dichloromethane
m-CPBA	meta-chloroperoxybenzoic acid
Cs_2CO_3	cesium carbonate
CO	carbon monoxide
CuI	copper(I) iodide
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane or ethylene dichloride
DIEA or DIPEA or *i*Pr_2NEt	N, N-diisopropylethylamine or Hünig's base
DMA	dimethylacetamide
DMF	dimethyl formamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
EtOAc or EA	ethyl acetate
EtOH	ethanol
EZ-Prep	CombiFlash® EZ Prep System by Teledyne ISCO
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
HBr	hydrobromic acid
HBPin	pinacolborane

Abbreviation	Meaning
HCl	hydrochloric acid
(HCHO)n	formaldehyde
HPLC	high performance liquid chromatography
h, hr, min, s	hour (h or hr), minute (min), second (s)
iPrOH	isopropyl alcohol
K_2CO_3	potassium carbonate
KOAc	potassium acetate
KOH	potassium hydroxide
Lawesson's reagent	2,4-Bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
LC/MS, LCMS or LC-MS	liquid chromatographic mass spectroscopy
LDA	lithium diisopropylamide
M	molarity
MeI	iododmethane
MeOH	methanol
MOM-Br	Bromomethyl methyl ether
MS	mass spectroscopy
MsCl	methanesulfonyl chloride
Mg_2SO_4	magnesium sulfate
N_2	nitrogen gas
$NaBH(OAc)_3$	sodium triacetoxyborohydride and sodium triacetoxyhydroborate
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
$NaNO_2$	sodium nitrite
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4HCO_3	ammonium bicarbonate
NH_4OH	ammonium hydroxide

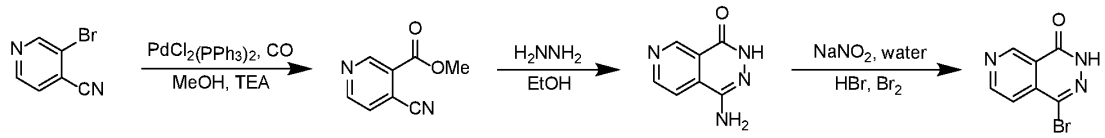
Abbreviation	Meaning
$N_2H_4H_2O$	hydrazine hydrate
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
$Pd(OAc)_2$	palladium(II) acetate
Pd/C^o	palladium on carbon
$Pd_2(dba)_3$ or Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PE	petroleum ether
PhMe	toluene
$POBr_3$	phosphoryl bromide or phosphorus oxybromide
prep-HPLC	preparative high performance liquid chromatography
RT or R.T. or rt	room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
sat.	saturated
SFC	supercritical fluid chromatography
SGC	solvating gas chromatography
SiO_2	silicon dioxide or silica gel
TBAF	tetra-n-butylammonium fluoride
t-Bu	tert-butyl
TEA, NEt_3, Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UPLC	Ultra Performance Liquid Chromatography
Pd XPhos G3	(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
Pd XPhos G4	methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II)

Intermediate 1a: 4-Chloropyrido[3,4-d]pyridazin-1(2H)-one



To a solution of 1,4-dichloropyrido[3,4-d]pyridazine (4 g, 20.0 mmol) in water (40 mL) was added concentrated HCl (8 mL, 12 mol/L). The reaction mixture was stirred at 90 °C for 1 h. After cooling, the precipitate (1.3 g) formed was filtered off and crystallized by acetic acid to give 4-chloropyrido[3,4-d]pyridazin-1(2H)-one (1 g, 5.5 mmol, 27%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 9.32 (d, *J* = 0.6 Hz, 1H), 9.10 (d, *J* = 5.2 Hz, 1H), 8.12 (dd, *J* = 5.2, 0.8 Hz, 1H).

Intermediate 1b: 1-Bromopyrido[3,4-d]pyridazin-4(3H)-one



Step 1. Methyl 4-cyanonicotinate

A mixture of 3-bromopyridine-4-carbonitrile (5 g, 27 mmol), TEA (45 mL,), $Pd(dppf)Cl_2$ (1.95 g, 2.68 mmol) in MeOH (40 mL) was stirred for 16 hours at 80 °C under CO (40 MPa). The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 5/1) to afford methyl 4-cyanonicotinate (2.8 g, 63% Yield) as a white solid. MS *m/z* 163.2 $[M+H]^+$.

Step 2. 1-Aminopyrido[3,4-d]pyridazin-4(3H)-one

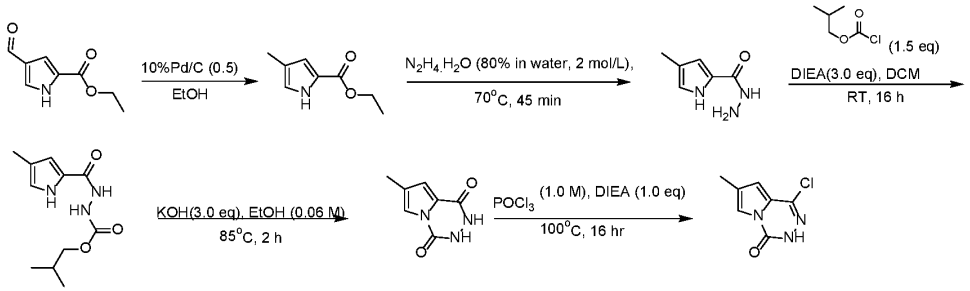
To a mixture of methyl 4-cyanonicotinate (2.8 g, 17 mmol) in MeOH (28 mL) was added hydrazine (6.9 g, 140 mmol). The resulting mixture was stirred at 70°C for 16 h. After cooling to rt, the mixture was filtered and the solid was washed with methanol and dried under vacuum to give 1-aminopyrido[3,4-d]pyridazin-4(3H)-one (2.7 g, 96% Yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 9.42 (s, 1H), 8.96 (d, J = 5.2 Hz, 1H), 8.03 (d, J = 5.2 Hz, 1H), 6.27 (s, 2H).

Step 3. 1-Bromopyrido[3,4-d]pyridazin-4(3H)-one

To a solution of 1-aminopyrido[3,4-d]pyridazin-4(3H)-one (8 g, 49.3 mmol) at 0 °C was added 40% aqueous HBr (120 mL) dropwise over 10 min. A solution of $NaNO_2$ (8.8 g, 128

mmol) in water (40 mL) was then added dropwise over 1 h and the mixture was stirred at 0 °C for 5 min. Br_2 (1.48 g, 9.25 mmol) was then added portion wise over 30 min and the mixture was heated at 70 °C for 1 h. Water (80 mL) was added and the resulting precipitate was collected by filtration, washed with water and dried under vacuum to give the title compound (7.0 g, 63%) as a white solid. MS *m/z* 226.1, 228.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 13.26 (s, 1H), 9.45 – 9.38 (m, 1H), 9.15 – 9.10 (m, 1H), 7.79 – 7.73 (m, 1H).

Intermediate 2a: 1-Chloro-7-methylpyrrolo[1,2-d][1,2,4]triazin-4(3H)-one



Step 1. Ethyl 4-methyl-1H-pyrrole-2-carboxylate

A mixture of ethyl 4-formyl-1H-pyrrole-2-carboxylate (10.3 g, 61.6 mmol, 1.0 eq.) and Pd/C (10%, 2.0 g) in EtOH (150 mL) was stirred at rt overnight under hydrogen (balloon). The mixture was filtered. The filtrate was concentrated under reduced pressure. The crude colorless oil (8.50 g, 55.5 mmol, 90% yield) was used in next step without further purification. MS *m/z* 154.2 $[M+H]^+$.

Step 2. 4-Methyl-1H-pyrrole-2-carbohydrazide

A solution of ethyl 4-methyl-1H-pyrrole-2-carboxylate (8.50 g, 55.5 mmol) in $N_2H_4H_2O$ (80%, 28 mL) was heated at 70°C for 45 min. After cooling to rt, the mixture was filtered, the filter cake was washed with EtOH and dried in vacuo to give 4-methyl-1H-pyrrole-2-carbohydrazide as a white solid (7.5 g, 97% yield). MS *m/z* 140.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ: 11.07 (s, 1H), 9.14 (s, 1H), 6.62 (s, 1H), 6.55 (s, 1H), 4.27 (s, 2H), 2.00 (s, 3H).

Step 3. Isobutyl 2-(4-methyl-1H-pyrrole-2-carbonyl) hydrazine-1-carboxylate

To a suspension of 4-methyl-1H-pyrrole-2-carbohydrazide (7.5 g, 53.9 mmol, 1.0 eq.) and DIEA (20.9 g, 161 mmol, 3.0 eq.) in DCM (540 mL) was added isobutyl carbonochloridate (11.1 g, 80.9 mmol, 1.5 eq.) dropwise with ice-water cooling bath. The mixture was stirred at rt overnight. Upon completion, the reaction mixture was diluted with DCM, washed with water and

brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to afford isobutyl 2-(4-methyl-1H-pyrrole-2-carbonyl) hydrazine-1-carboxylate (12.0 g, 93%) as a white solid. MS *m/z* 240.2 $[M+H]^+$.

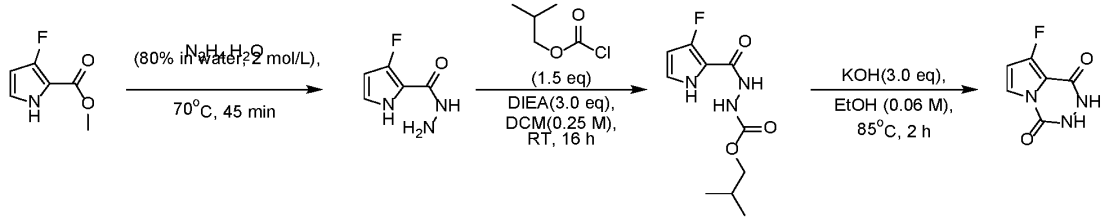
Step 4. 7-Methyl-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione

To a solution of isobutyl 2-(4-methyl-1H-pyrrole-2-carbonyl) hydrazine-1-carboxylate (12.0 g, 50.2 mmol, 1.0 eq.) in EtOH (840 mL) was added KOH (8.40 g, 151 mmol, 3.0 eq.). The mixture was stirred at 85°C for 2 h. The reaction mixture was cooled to room temperature and filtered, the filter cake was washed with EtOH. The solid was dissolved with water, and adjusted to pH = 4 with 1M HCl. The precipitate was filtered, the filter cake was washed with water and dried in vacuo to afford 7-methyl-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (4.0 g, 48% yield) as a white solid. MS *m/z* 166.2 $[M+H]^+$.

Step 5. 1-Chloro-7-methylpyrrolo[1,2-d][1,2,4]triazin-4(3H)-one

To a solution of 7-methyl-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (4.0 g, 24.2 mmol, 1.0 eq.) in $POCl_3$ (1.0 M, 25 mL) was added DIEA (3.12 g, 24.2 mmol, 1.0 eq.) dropwise with ice cooling bath. The mixture was stirred at 100°C for 16h. The reaction mixture was cooled to room temperature, concentrated. The residue was carefully poured into ice water, adjusted pH=8 with sat $NaHCO_3$ aq. The mixture was extracted with DCM: MeOH (10:1, 100 mLx3), dried over Na_2SO_4, concentrated, purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford 1-chloro-7-methylpyrrolo[1,2-d][1,2,4]triazin-4(3H)-one (2.0 g, 45% yield) as a white solid. MS *m/z* 184.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ: 12.43 (s, 1H), 7.66 (s, 1H), 6.75 (s, 1H), 2.23 (s, 3H).

Intermediate 2b: 8-Fluoro-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione



Step 1. 3-Fluoro-1H-pyrrole-2-carbohydrazide

A mixture of $N_2H_4 \cdot H_2O$ (80% in water, 18 mL) and methyl 3-fluoro-1H-pyrrole-2-

carboxylate (3.14 g, 20.0 mmol) was stirred at 70 °C for 45 minutes. After cooling to rt, the precipitate was filtered, the filter cake was washed with water and dried under vacuum to obtain 3-fluoro-1H-pyrrole-2-carbohydrazide (2.30 g, 73%) as a white solid. MS *m/z* 144.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 11.31 (s, 1H), 8.55 (s, 1H), 6.74 (dd, *J* = 4.6, 3.0 Hz, 1H), 5.97 (d, *J* = 3.0 Hz, 1H), 4.39 (s, 2H).

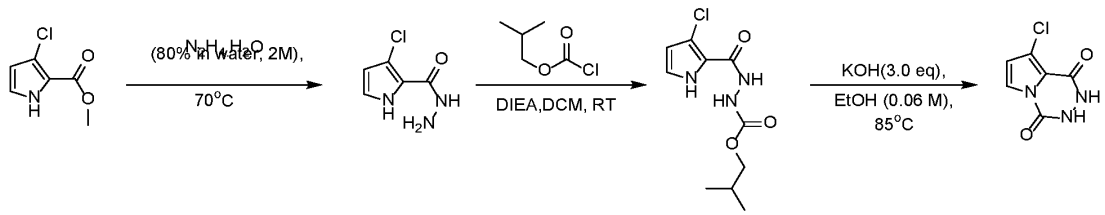
Step 2. Isobutyl 2-(3-fluoro-1H-pyrrole-2-carbonyl)hydrazine-1-carboxylate

To a solution of 3-fluoro-1H-pyrrole-2-carbohydrazide (2.15 g, 15.0 mmol, 1.0 eq.) in DCM (60 mL) was added DIPEA (5.80 g, 45.0 mmol, 3.0 eq.). Isobutyl carbonochloridate (3.00 g, 22.5 mmol, 1.5 eq.) was added to the mixture slowly. The mixture was stirred at rt for 16 h. After concentration, the mixture was diluted with EtOAc (200 mL). The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford isobutyl 2-(3-fluoro-1H-pyrrole-2-carbonyl)hydrazine-1-carboxylate (2.44 g, 66.7% yield) as yellow solid. MS *m/z* 244.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 11.46 (s, 1H), 9.18 (s, 1H), 9.09 (s, 1H),6.82 (d, *J* = 4.4 Hz, 1H), 6.01 (d, *J* = 2.5 Hz, 1H), 3.82 (d, *J* = 6.6 Hz, 2H), 2.02 – 1.67 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 6H).

Step 3. 8-Fluoro-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione

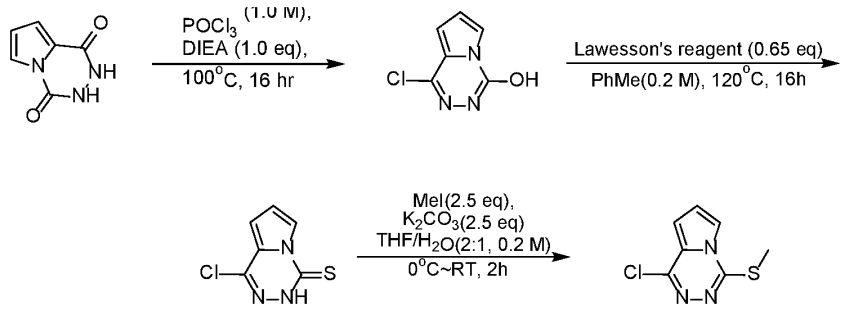
To a solution of isobutyl 2-(3-fluoro-1H-pyrrole-2-carbonyl)hydrazine-1-carboxylate(2.44 g, 10.0 mmol, 1.0 eq.) in EtOH (60 mL) was added KOH (1.68 g, 30 mmol, 3 eq.). The mixture was stirred at 85 °C for 2 h. After cooling to rt, the mixture was concentrated. The residue was diluted with water (50 mL) and adjusted to pH to 6-7 with 1M HCl. The precipitates were filtered, the filter cake was washed with water and dried under vacuum to obtain 8-fluoro-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (1.16 g, 68.7% yield) as brown solid. MS *m/z* 168.0 $[M-H]^-$, ^1H NMR (400 MHz, DMSO-d6) δ: 11.52 (s, 2H), 7.57 (t, *J* = 4.1 Hz, 1H), 6.68 (d, *J* = 3.4 Hz, 1H).

Intermediate 2c: 8-Chloro-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione



The title compound was prepared in analogous manner according to the procedure of Intermediate 2b, using methyl 3-chloro-1H-pyrrole-2-carboxylate in place of 3-fluoro-1H-pyrrole-2-carboxylate in step 1. MS m/z 186.0, 188.0 [M+H]+.

Intermediate 2d: 1-chloro-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine



Step 1. 1-Chloropyrrolo[1,2-d][1,2,4]triazin-4-ol

To a stirred solution of 2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (2 g, 13.2 mmol) in $POCl_3$ (60 mL) was added DIEA (1.84 g, 14.2 mmol). The reaction mixture was heated at 100 °C for 16 h. After cooling to rt, the mixture was concentrated under reduced pressure to give a residue. The residue was diluted with cold saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and evaporated under reduced pressure. The crude was further triturated with DCM to give the title compound 1-chloropyrrolo[1,2-d][1,2,4]triazin-4-ol (0.867 g, 38.6% Yield) as an off-white solid, which was used to next step without further purification. MS *m/z* 169.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 12.54 (s, 1H), 7.88 - 7.87 (m, 1H), 6.92 - 6.89 (m, 2H).

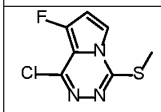
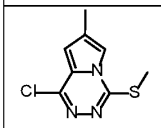
Step 2. 1-Chloropyrrolo[1,2-d][1,2,4]triazine-4(3H)-thione

To a solution of 1-chloropyrrolo[1,2-d][1,2,4]triazin-4-ol (30.0 g, 177 mmol) in toluene (1200 mL) was added Lawesson's Reagent (46.2 g, 114 mmol). The reaction was stirred at 120 °C for 16 h. The mixture was diluted with H_2O (1.5 L), acidified with aqueous HCl (1 M) till pH = 3 and extracted with EA. The EA layer was wash with sat. $NaHCO_3$ aqueous solution (1 L) and brine (1 L), then dried over anhydrous Na_2SO_4 and concentrated to give crude 1-chloro-3H-pyrrolo[1,2-d][1,2,4]triazine-4-thione (crude 35.0 g, overweight), which was used to next step without further purification. MS *m/z* 184.1 $[M-H]^-$.

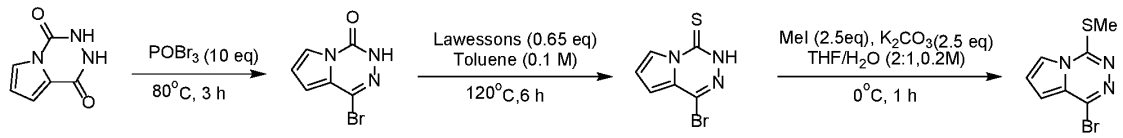
Step 3. 1-Chloro-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine

To a solution of 1-chloro-3H-pyrrolo[1,2-d][1,2,4]triazine-4-thione (crude 35.0 g, 189 mmol) in THF (600 mL) and water (300 mL) was added K_2CO_3 (65.2 g, 472 mmol), followed by iodomethane (68.6 g, 483 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then diluted with water and extracted with EA (3 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 50/1 to 20/1) to afford title product 1-chloro-4-methylsulfanyl-pyrrolo[1,2-d][1,2,4]triazine (21.8 g, 109 mmol, 57.9% for two steps Yield) as a white solid. MS *m/z* 200.0 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 7.83 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 7.16 (dd, J = 4.0 Hz, 2.8 Hz, 1H), 7.11 (dd, J = 4.0 Hz, 1.2 Hz, 1H), 2.81 (s, 3H).

The intermediates below were prepared according to the procedure of Intermediate 2d by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	From Intermediate 2b; ^1H NMR (400 MHz, DMSO-d6) δ: 7.73 – 7.71 (m, 1H), 7.14 (d, J = 3.2 Hz, 1H), 2.79 (s, 3H).
	From Intermediate 2a; ^1H NMR (400 MHz, DMSO–d6) δ: 7.65 (s, 1H), 6.94 (s, 1H), 2.79 (s, 1H), 2.33 (s, 1H).

Intermediate 2e: 1-Bromo-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine



Step 1. 1-Bromopyrrolo[1,2-d][1,2,4]triazin-4(3H)-one

A mixture of 2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (30.0 g, 0.199 mol, 1.0 eq.) and $POBr_3$ (570 g, 1.99 mol, 10 eq.) was heated at 80°C for 3 hours. The hot reaction mixture was slowly pour into a stirring mixture of ice and aqueous sat. $NaHCO_3$. The mixture was neutralized with solid $NaHCO_3$ to pH ~ 7 and extracted with a mixture of MeOH/DCM (1 L x 2, 1:10). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was triturated with DCM, filtered and washed with DCM. The solid was dried under vacuum to afford 1-bromopyrrolo[1,2-d][1,2,4]triazin-4(3H)-one (21.9

g, 0.103 mol, 51.8% yield) as a pink solid. MS *m/z* 214.0, 215.9 $[M+H]^+$.

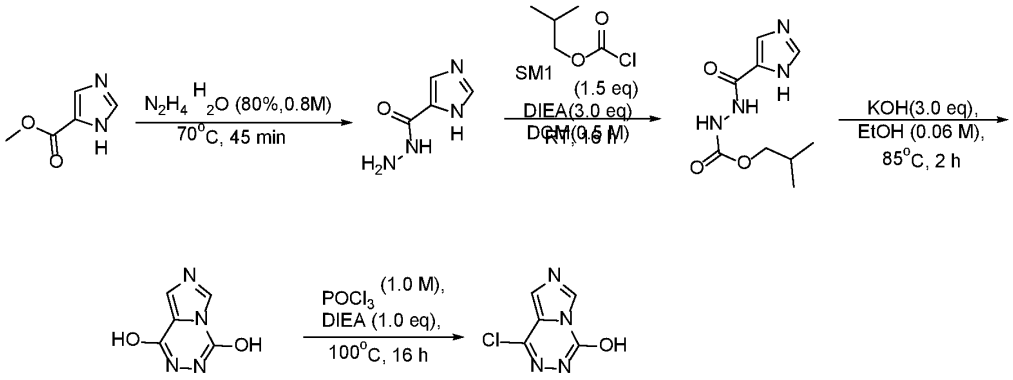
Step 2. 1-Bromopyrrolo[1,2-d][1,2,4]triazine-4(3H)-thione

To a solution of 1-bromopyrrolo[1,2-d][1,2,4]triazin-4(3H)-one (10.0 g, 46.7 mmol, 1.0 eq.) in DMSO (472 mL) was added Lawesson's Reagent (12.4 g, 30.7 mmol, 0.65 eq.). The reaction mixture was heated at 120°C for 6 hours. The reaction mixture was cooled to room temperature, diluted with aqueous saturated $NaHCO_3$ and extracted with EtOAc (300 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to afford 1-bromopyrrolo[1,2-d][1,2,4]triazine-4(3H)-thione as a white solid (1.56 g, 6.78 mmol, 14.5% yield). MS *m/z* 228.0, 230.0 $[M-H]^-$. ^1H NMR (400Hz, DMSO-d6) δ: 14.15 (s, 1H), 8.23 (dd, J = 2.9, 1.4 Hz, 1H), 7.10 (dd, J = 3.7, 3.1 Hz, 1H), 7.06 (dd, J = 3.9, 1.4 Hz, 1H).

Step 3. 1-Bromo-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine

To a mixture of 1-bromopyrrolo[1,2-d][1,2,4]triazine-4(3H)-thione (2.00 g, 8.69 mmol, 1.0 eq.) and K_2CO_3 (3.00 g, 21.7 mmol, 2.5 eq.) in THF (43 mL) and water (21 mL) was added iodomethane (1.35 mL, 2.28 g/mL, 21.7 mmol, 2.5 eq.) dropwise at 0°C. The reaction was stirred at 0°C for 1 hour. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to afford 1-bromo-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (1.40 g, 5.74 mmol, 66.1% yield) as a white solid. MS *m/z* 243.9, 246.0 $[M+H]^+$. ^1H NMR (400Hz, DMSO-d6) δ: 7.83 (dd, *J* = 2.8, 1.0 Hz, 1H), 7.15 (dd, *J* = 4.0, 2.8 Hz, 1H), 7.03 (dd, *J* = 4.0, 1.0 Hz, 1H), 2.79 (s, 3H).

Intermediate 3: 1-Chloroimidazo[1,5-d][1,2,4]triazin-4-ol



Step 1. 1H-Imidazole-5-carbohydrazide

A solution of methyl 1H-imidazole-5-carboxylate (21 g, 166.5 mmol) in hydrazinium hydroxide solution (80%, 260 mL) was stirred at 70°C in sealed tube for 45 mins. After cooling to room temperature, it was concentrated in vacuo to get the crude product, which was triturated with ether and filtered to provide the title compound as white solids (19.9 g, yield 94.8%). MS *m/z* 127.2 $[M+H]^+$.

Step 2. Isobutyl 2-(1H-imidazole-5-carbonyl)hydrazine-1-carboxylate

To a solution of 1H-imidazole-5-carbohydrazide (19.9 g, 157.9 mmol) in DCM (200 mL) was added N,N-Diisopropylethylamine (61.1 g, 473.7 mmol) and isobutyl carbonochloridate (32.4 g, 236.9 mmol). The mixture was stirred rt for 16 h. After that, the reaction was quenched with water (500 mL), extracted with DCM (3 x 500 mL). The combined organic layers were concentrated in vacuo to get a crude. The crude was purified by column (DCM/MeOH=15:1) to provide the title compound as white solids (18.0 g, yield 50.4%). MS *m/z* 227.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.72 (s, 2H), 3.90 (d, *J* = 6.4 Hz, 2H), 2.01-1.81 (m, 1H), 0.95 (d, *J* = 5.5 Hz, 6H).

Step 3. Imidazo[1,5-d][1,2,4]triazine-1,4-diol

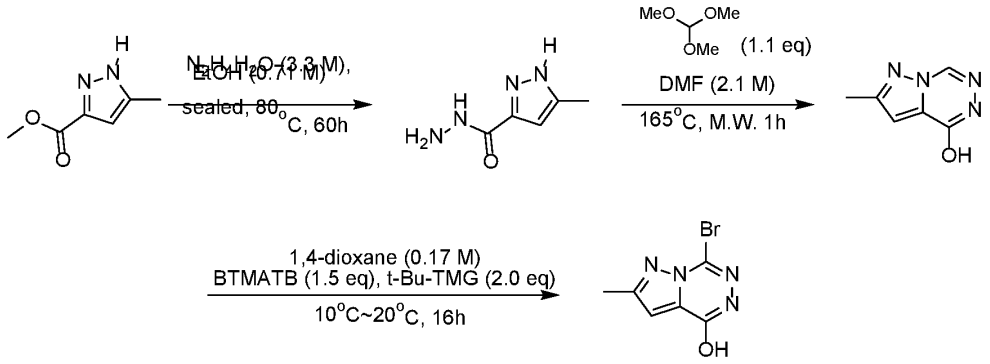
To a mixture of isobutyl 2-(1H-imidazole-5-carbonyl) hydrazine-1-carboxylate (1.0 g, 4.42 mmol) in ethanol (10 mL) was added KOH (743 mg, 13.26 mmol). The reaction mixture was heated at 85°C for 16 h. After cooling to room temperature, it was concentrated in vacuo to get a crude. The crude was added con. HCl solution to adjust pH to 6 and extracted with (DCM/MeOH=10:1), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to get the title compound as brown solids (500 mg, yield 74.4%), which was used

directly in the next step. MS *m/z* 153.2 $[M+H]^+$.

Step 4. 1-Chloroimidazo[1,5-d][1,2,4]triazin-4-ol

A solution of imidazo [1,5-d] [1,2,4] triazine-1,4-diol (500 mg, 3.29 mmol) in Phosphorus oxychloride (5 mL) was added DIPEA (933 mg, 7.23 mmol) under ice bath. The mixture was stirred at 115°C for 16 h. After cooling to room temperature, it was concentrated in vacuo to get a crude. The crude was added DCM (20 mL) and the solution was slowly poured into excess sodium bicarbonate ice water solution, and a large number of air bubbles were generated, the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were concentrated to obtain the crude product, the crude product was triturated with PE/EA (1:1) to provide the title compound as brown solid (120 mg crude). MS *m/z* 171.2 $[M+H]^+$.

Intermediate 4a: 7-Bromo-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol



Step 1. 5-Methyl-1H-pyrazole-3-carbohydrazide

Hydrazine hydrate (54 mL, 1.032 g/mL, 1.11 mol, 6.2 eq.) was added to a solution of methyl 5-methyl-1H-pyrazole-3-carboxylate (25.0 g, 0.178 mol, 1.0 eq.) in EtOH (250 mL). The mixture was sealed and heated at 80 °C for 60 h. The reaction mixture was cooled to room temperature. The solvent was evaporated in vacuo. The crude product was treated with a 1/1 mixture of water/MeOH, filtered and the filter cake was washed with water. The solid was dried under vacuum to afford 5-methyl-1H-pyrazole-3-carbohydrazide (21.7 g, 0.155 mol, 87.0% yield) as a white solid. MS *m/z* 141.1 $[M+H]^+$.

Step 2. 2-Methylpyrazolo[1,5-d][1,2,4]triazin-4-ol

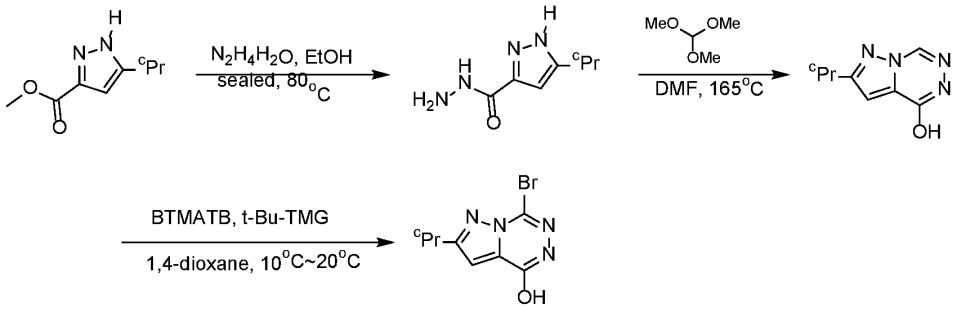
A mixture of 5-methyl-1H-pyrazole-3-carbohydrazide (3.00 g, 21.4 mmol, 1.0 eq.) and

trimethoxymethane (2.57 mL, 0.970 g/mL, 23.5 mmol, 1.1 eq.) in DMF (10 mL) was sealed in a tube. The reaction mixture was stirred at 165°C for 1 hour under microwave then cooled to room temperature. The precipitate was collected by filtration, washed with EtOH and dried under vacuum to afford 2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (1.70 g, 11.3 mmol, 52.9% yield) as a white solid. MS *m/z* 149.2 $[M-H]^-$.

Step 3. 7-Bromo-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol

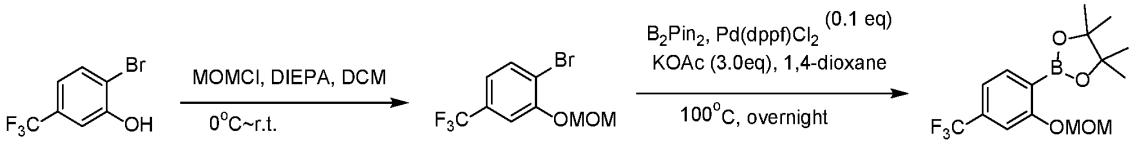
Benzyltrimethylammonium tribromide (26.5 g, 68.0 mmol, 1.5 eq.) was added in portions to a stirred solution of 2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (6.80 g, 45.3 mmol, 1.0 eq.) and 2-(tert-butyl)-1,1,3,3-tetramethylguanidine (18.3 mL, 0.85 g/mL, 90.6 mmol, 2.0 eq.) in 1,4-dioxane (290 mL) under N_2 at 10 °C. Once the addition was completed the mixture was warmed to 20 °C and stirred at this temperature for 16 hours. Then the mixture was quenched with a mixture of aqueous sat. $Na_2S_2O_3$ and aqueous sat. $NaHCO_3$ and then extracted with EtOAc (150 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was triturated with EtOAc, filtered and washed with EtOAc. The solid was dried under vacuum to afford 7-bromo-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (7.60 g, 33.3 mmol, 73.6% yield) as an off-white solid. MS *m/z* 229.0, 230.9 $[M+H]^+$. ^1H NMR (400Hz, DMSO-d6) δ: 12.60 (s, 1H), 7.15 (s, 1H), 2.42 (s, 3H).

Intermediate 4b: 7-Bromo-2-cyclopropylpyrazolo[1,5-d][1,2,4]triazin-4-ol



The title compound was prepared in analogous manner according to the procedure of Intermediate 4a, using methyl 5-cyclopropyl-1H-pyrazole-3-carboxylate in place of 5-methyl-1H-pyrazole-3-carboxylate in step 1. MS *m/z* 255.0, 257.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (bs, 1H), 6.94 (s, 1H), 2.15-2.17 (m, 1H), 1.12-1.15 (m, 2H), 0.92-0.94 (m, 2H).

Intermediate 5a: 2-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



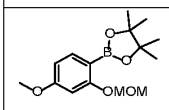
Step 1. 1-Bromo-2-(methoxymethoxy)-4-(trifluoromethyl)benzene

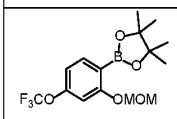
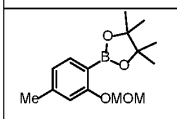
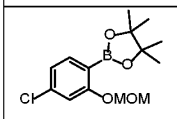
To a cold solution of 2-bromo-5-(trifluoromethyl)phenol (2.20 g, 8.9 mmol) in DCM (7.2 mL) was added DIPEA (1.9 mL, 1.2 eq.), followed by addition of chloro(methoxy)methane (0.8 mL, 9.8 mmol, 1.1 eq.). The reaction mixture was warmed to rt, then stirred overnight. The reaction was quenched by ice water and extracted with EtOAc. The organics were washed with water and brine, dried over sodium sulfate and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexane to provide 1-bromo-2-(methoxymethoxy)-4-(trifluoromethyl)benzene (1.9 g, 77 % yield). ^{1}H NMR (acetone-d6) δ: 7.70 (d, J=8.3 Hz, 1H), 7.38 (s, 1H), 7.13-7.19 (m, 1H), 5.29 (s, 2H), 3.37 (s, 3H).

Step 2. 2-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

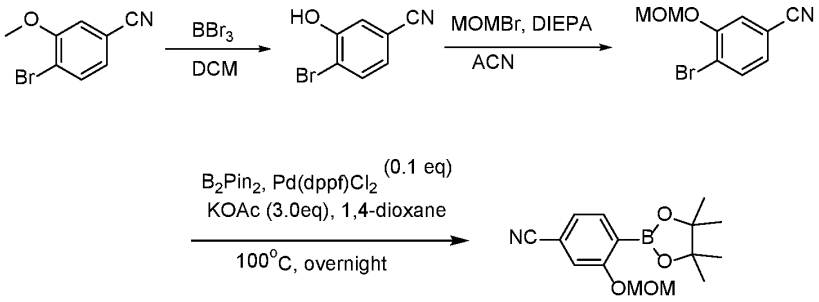
A mixture of 1-bromo-2-(methoxymethoxy)-4-(trifluoromethyl)benzene (1.06 g, 3.72 mmol, 1.0 eq.), bis(pinacolato)diboron (1.95 g, 7.4 mmol, 2.0 eq.), Pd(dppf)Cl_2 (153 mg, 0.05 eq.) and KOAc (1.13 g, 11 mmol, 3.0 eq.) in dioxane (12 mL) was heated at 100°C under Ar for 16 hr. After cooling, the reaction mixture was diluted with DCM, filtered through celite and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexane to provide 2-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.10 g, 89 % yield). ^{1}H NMR (acetone-d6) δ: 7.81 (d, J=7.6 Hz, 1H), 7.33-7.39 (m, 2H), 5.31 (s, 2H), 3.51 (s, 3H), 1.28-1.39 (s, 12H).

The intermediates below were prepared according to the procedure of Intermediate 5a by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	^{1}H NMR (400 MHz, DMSO-d6) δ 7.50 (d, J= 8.8 Hz, 1H), 6.61 – 6.56 (m, 2H), 5.15 (s, 2H), 3.75 (s, 3H), 3.41 (s, 3H), 1.26 (s, 12H).

Structure	Spectral Data
	^{1}H NMR (400MHz, DMSO–d6) δ: 7.65(d, J = 8.4 Hz,1H), 7.05 –7.04 (m,1H), 7.00 –6.98 (m, 1H), 5.22 (s, 2H), 3.41 (s, 3H), 1.28 (s, 12H).
	^{1}H NMR (400 MHz, DMSO-d6) δ: 7.46 (d, J = 7.6 Hz, 1H), 6.89 (s, 1H), 6.83 (d, J = 7.6 Hz, 1H), 5.14 (s, 2H), 3.41 (s, 3H), 2.30 (s, 3H),1.27 (s, 12H).
	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (t, J= 6.8 Hz, 1H), 7.05 (d, J= 1.8 Hz, 1H), 7.00 (dd, J= 8.0, 1.8 Hz, 1H), 5.19 (d, J= 8.6 Hz, 2H), 3.49 (d, J= 10.9 Hz, 3H), 1.34 (s, 12H).

Intermediate 5b: 3-(Methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile



Step 1. 4-Bromo-3-hydroxybenzonitrile

To a solution of 4-bromo-3-methoxybenzonitrile (5 g, 23.6 mmol) was added BBr_3 (1 M in DCM, 50 mL). The reaction was stirred at R.T for 16 h, monitored by TLC and LCMS. After reaction, solvent was removed and residue was purified via flash column chromatography to give 4-bromo-3-hydroxybenzonitrile (2.4 g, 51% Yield). MS *m/z* 198.0 $[M+H]^+$.

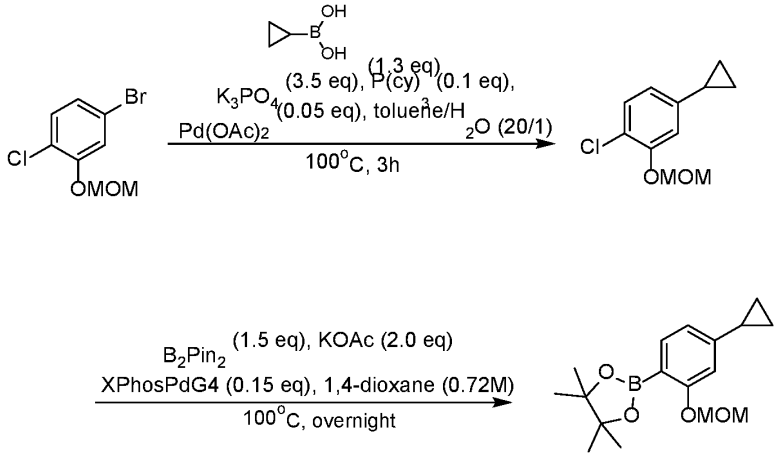
Step 2. 4-Bromo-3-(methoxymethoxy)benzonitrile

To a solution of 4-bromo-3-hydroxybenzonitrile (2.4 g, 12 mmol) in CH_3CN (24 mL) was added DIEA (7.8 g, 60 mmol) and MOM-Br (2 g, 16 mmol). The mixture was stirred at R.T. for 2 h, monitored by TLC and LCMS. After that, the mixture was poured into H_2O, extracted with EA, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to give 4-bromo-3-(methoxymethoxy)benzonitrile (2 g, 70% Yield). MS *m/z* 242.0 $[M+H]^+$.

Step 3. 3-(Methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile

A solution of 4-bromo-3-(methoxymethoxy)benzonitrile (1 g, 4.13 mmol), bis(pinacolato)diboron (1.92 g, 4.92 mmol), potassium acetate (819 mg, 8.26 mmol), and $Pd(dppf)Cl_2$ (318 mg, 0.41 mmol) in 1,4-dioxane (10 mL) was stirred at 90°C under N_2 for 16h. After reaction, the residue was purified by flash column chromatography to give 3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.1 g, 92% Yield). MS *m/z* 290.0 $[M+H]^+$.

Intermediate 5c: 2-(4-Cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 1-Chloro-4-cyclopropyl-2-(methoxymethoxy)benzene

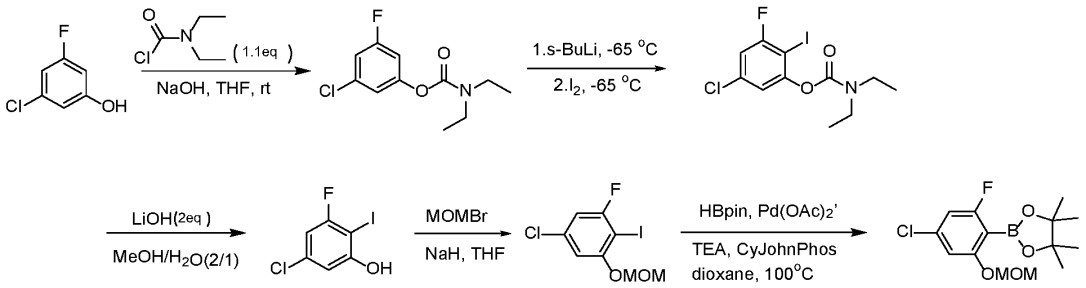
A mixture of 4-bromo-1-chloro-2-(methoxymethoxy)benzene (prepared according to the procedure of Intermediate 5a, step 1, 1.5 g, 6.0 mmol), cyclopropylboronic acid (670 mg, 7.8 mmol), potassium phosphate tribasic (4.5 g, 21 mmol), tricyclohexylphosphine (170 mg, 0.60 mmol) and palladium(ii) acetate (67 mg, 0.30 mmol) in water (2 mL) and toluene (40 mL) was stirred at 100°C for 3 hours under N_2. After cooling to rt. the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated to give a residue that was purified by flash chromatography on silica gel (EtOAC in PE=0%) to afford the product.1-chloro-4-cyclopropyl-2-(methoxymethoxy)benzene (780 mg, 61% Yield).

Step 2. 2-(4-Cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane

A solution of 1-chloro-4-cyclopropyl-2-(methoxymethoxy)benzene (780 mg, 3.7 mmol), bis(pinacolato)diboron (1.4 g, 5.5 mmol), potassium acetate (720 mg, 7.3 mmol,), XPhos Pd G4 (473 mg, 0.54 mmol,) in 1,4-dioxane (5 mL) was stirred at 100°C for 16 hours under N_2. After reaction, the mixture was poured into H_2O, extracted with DCM. The combined organic phase was dried over Na_2SO_4 and concentrated to give the crude product 2-(4-cyclopropyl-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 g) which was used in the next step directly. ^{1}H NMR (400 MHz, DMSO–d6) δ: 7.43 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.68 (d, J =8.8 Hz, 1H), 5.14 (s, 2H), 3.41 (s, 3H), 1.93 – 1.82 (m, 1H), 1.27 (s, 12H), 1.00 – 0. 89 (m, 2H), 0.73 – 0.59 (m, 2H).

Intermediate 5d: 2-(4-Chloro-2-fluoro-6-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 3-Chloro-5-fluorophenyl diethylcarbamate

To a solution of 3-chloro-5-fluorophenol (1.46 g, 10 mmol) in doxane (15 mL) was added diethylcarbamic chloride (1.36 g, 10 mmol) and NaOH (800 mg, 20 mmol). The mixture was stirred at rt for 16 h, monitored by LCMS. Water was added, and the mixture was extracted with EA. The organic layers were washed by H_2O and brine, then dried and concentrated under vacuum to give residue which was purified by SGC (PE/EtOAc = 10:1) to give 3-chloro-5-fluorophenyl diethylcarbamate (2.2 g, 8.9 mmol, 89.8% Yield) as a pale yellow oil.

Step 2. 5-Chloro-3-fluoro-2-iodophenyl diethylcarbamate

To a solution of 3-chloro-5-fluorophenyl diethylcarbamate (2.2 g, 8.9 mmol) in THF (25 ml) was added s-BuLi (5.4 mL, 13.4 mmol, 2.5 mol/L) at -78 °C. The mixture was stirred at -78 °C for 1.5 h and then a solution of I_2 (2.50 g, 1.1 eq) in THF (10 mL) was added in. This mixture was stirred at -78 °C for another 0.5 h. After that, the reaction was quenched with HCl (1 M), and

warmed to room temperature. The mixture was diluted with aqueous $Na_2S_2O_3$ solution, extracted with EtOAc. The combined organic was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue which was purified by SGC (hexane/EtOAc= 20:1) to get 5-chloro-3-fluoro-2-iodophenyl diethylcarbamate (2.3 g, 6.2 mmol, 69.1% Yield) as colorless oil. MS *m/z* 371.8 $[M+H]^+$.

Step 3. 5-Chloro-3-fluoro-2-iodophenol

To a solution of 5-chloro-3-fluoro-2-iodophenyl diethylcarbamate (2.3 g, 6.2 mmol) in MeOH: H_2O=2:1 (24 mL) was added LiOH.H_2O (525 mg, 12.5 mmol). The mixture was stirred at 60 °C for 16 h, monitored by LCMS. After that, 1M HCl was added to pH =7 and the mixture was extracted with EA. The organic layers were washed by H_2O and brine, then dried and concentrated under vacuum to give residue which was purified by column chromatography (PE/EtOAc = 10:1) to give 5-chloro-3-fluoro-2-iodophenol (1.5 g, 5.5 mmol, 89.3% Yield) as colorless oil. MS *m/z* 270.9 $[M-H]^-$.

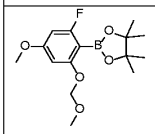
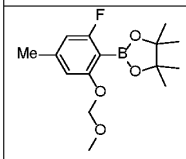
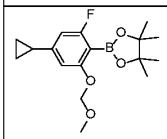
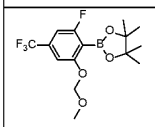
Step 4. 5-Chloro-1-fluoro-2-iodo-3-(methoxymethoxy)benzene

To a solution of 5-chloro-3-fluoro-2-iodophenol (540 mg, 2 mmol) in THF (6 mL) was added NaH (72 mg, 3 mmol) at 0 °C. The reaction mixture was stirred at rt for 1h, MOMBr (375 mg, 3 mmol) was added, stirred at rt for 0.5h. After that, water was added to quench the reaction. The mixture was extracted with EA. The organic layers was washed by H_2O and brine, then dried and concentrated under vacuum to give residue which was purified by SGC (PE/EtOAc = 10:1) to give 5-chloro-1-fluoro-2-iodo-3-(methoxymethoxy)benzene (550 mg, 1.73 mmol, 87 % yield) as colorless oil.

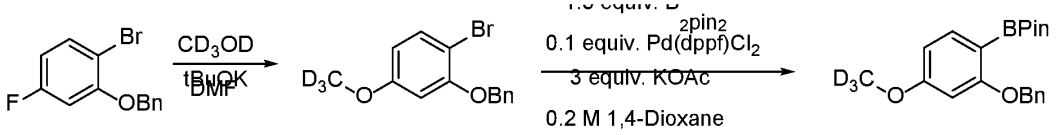
Step 5. 2-(4-Chloro-2-fluoro-6-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of 5-chloro-1-fluoro-2-iodo-3-(methoxymethoxy)benzene (550 mg, 1.73 mmol) in 1,4-dioxane (6 ml) was added $Pd(OAc)_2$ (55 mg, 0.24 mmol), 2-dicyclohexylphosphino)biphenyl (145 mg, 0.42 mmol), TEA (1.24 g, 12.1 mmol) and HBPin (1.1 g, 8.7 mmol), The reaction was heated to 80 degrees under nitrogen protection and stirred for 16h, monitored by LCMS. After that, the mixture was concentrated to give a residue which was purification by SGC (PE/EtOAc = 10:1) to give crude 2-(4-chloro-2-fluoro-6-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg) as black oil. ^1H NMR (400 MHz, DMSO-d6) δ 6.99 (s, 2H), 5.22 (s, 2H), 3.38 (s, 3H), 1.30 (s, 12H).

The intermediates below were prepared according to the procedure of Intermediate 5d by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	^{1}H NMR (400 MHz, DMSO-d6) δ 6.48 – 6.35 (m, 2H), 5.16 (s, 2H), 3.76 (s, 3H), 3.39 (s, 3H), 1.28 (s, 12H).
	^{1}H NMR (400 MHz, DMSO-d6) δ 6.72 (s, 1H), 6.61 (d, J = 11.6 Hz, 1H), 5.16 (s, 2H), 3.39 (s, 3H), 2.24 (s, 3H), 1.29 (s, 12H)
	^{1}H NMR (400 MHz, DMSO-d6) δ 6.62 (s, 1H), 6.44 (d, J = 9.6Hz, 1H), 5.16 (s, 2H), 3.38 (s, 3H), 1.94-1.87 (m, 1H), 1.28 (s, 12H), 0.99-0.91 (m, 2H), 0 .72-0.65 (m, 2H).
	^{1}H NMR (400 MHz, DMSO–d6) δ 7.25 – 7.23 (m, 2H), 5.31 (s, 2H), 3.39 (s, 3H), 1.32 (s, 12H).

Intermediate 5e: 2-(2-(Benzyloxy)-4-(methoxy-d3)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



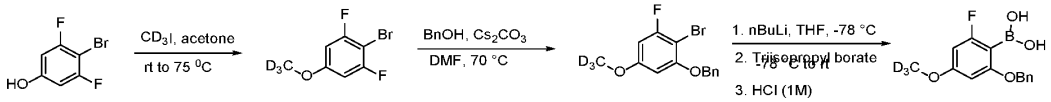
Step 1: 2-(Benzyloxy)-1-bromo-4-(methoxy-d3) benzene

To a suspension of *t*-BuOK (3.40 g, 30 mmol, 3.9 eq.) in DMF (25 ml) was added MeOH-d4 (1.90 ml, 46 mmol, 6 eq.) dropwise under nitrogen at 0 °C. The reaction mixture was allowed to stir at 0 °C for 15 mins. A solution of 2-(benzyloxy)-1-bromo-4-fluorobenzene (2.10 g, 7.60 mmol) in DMF (5 mL) was added into the reaction and the reaction mixture was heated to 80 °C for 20 h. The reaction was quenched with saturated NH_4Cl aqueous solution. Then reaction mixture was extracted with EA and washed with brine and dried over $MgSO_4$ and concentrated to dryness. The resulting oily residue was purified by chromatography on SiO_2 (EtOAc : Hexane, 0 to 75%) to afford the desired product (2.20 g, 90%) as a colorless oil. MS *m/z* 297.2 $[M+H]^+$.

Step 2. 2-(2-(Benzyloxy)-4-(methoxy-d3)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

2-(Benzyloxy)-1-bromo-4-(methoxy-d3)benzene (1.00 g, 3.41 mmol), B_2Pin_2 (1.30 g, 5.12 mmol, 1.5 eq.), KOAc (1.00 g, 10.2 mmol, 3 eq.) and $Pd(dppf)Cl_2$ (0.26 g, 0.34 mmol, 0.1 eq.) was added in a vial and evacuated and backfilled with Ar before diluted with dioxane (17 mL). And the reaction was sparged with Ar for 5 min then was heated to 90 °C for 3 h. The reaction was cooled to rt and diluted with EtOAc. The organic phase was washed with water, brine and dried over Mg_2SO_4, filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc : Hexane, 0 to 40%) gave a pale yellow oil (759 mg, 65%). MS *m/z* 344.1 $[M+H]^+$.

Intermediate 5f: 2-(2-(Benzyloxy)-6-fluoro-4-(methoxy-d3)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1: 2-Bromo-1,3-difluoro-5-(trideuteriomethoxy)benzene

To a 250-mL round-bottom flask equipped with a magnetic stir bar under argon atmosphere was added 4-bromo-3,5-difluoro-phenol (4.97 g, 23.8 mmol) and acetone (120 mL, 5 L/mol). Potassium carbonate (6.8 g, 49 mmol, 2.1 equiv) was added at room temperature and the suspension was stirred vigorously. Iodomethane-d_3 (1.9 mL, 29.8 mmol, 1.25 equiv) was added slowly via syringe, and the reaction mixture was heated to 75 °C for 3 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated under reduced pressure (40 °C, 100 mmHg) and the resulting oil was taken up in diethyl ether. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over sodium sulfate, filtered, and concentrated to afford the crude product. Purification by column chromatography (silica, gradient 0% to 50% EtOAc in hexanes) afforded 2-bromo-1,3-difluoro-5-(trideuteriomethoxy)benzene (4.17 g, 78%) as a clear, colorless oil. ^1H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 9.0 Hz, 2H).

Step 2. 1-Benzyloxy-2-bromo-3-fluoro-5-(trideuteriomethoxy)benzene

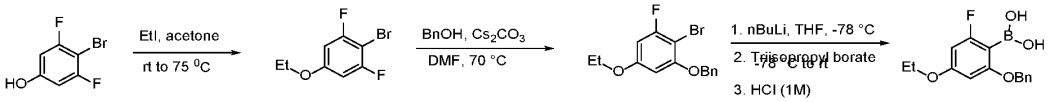
To a 120-mL test-tube equipped with a magnetic stir bar and a Teflon-lined cap was added 2-bromo-1,3-difluoro-5-(trideuteriomethoxy)benzene (2.55 g, 11.3 mmol) and DMF (22 mL, 2 L/mol). Cesium carbonate (7.2 g, 22 mmol, 2.0 equiv) was added and the mixture was

stirred to even suspension. Benzyl alcohol (2.3 mL, 2.4 g, 22 mmol, 2.0 equiv) was added and the mixture was heated to 70 °C. After 16 h the reaction had reached about 80% conversion as judged by LC-MS, so an additional 2 equivalents of cesium carbonate and benzyl alcohol were added. After an additional 8 h, the reaction was deemed complete by LC-MS. Cesium carbonate was removed by filtration through a plastic frit, and the filtrate was loaded directly onto silica. Chromatography (silica, gradient 0% to 40% dichloromethane in hexanes) afforded 1-benzyloxy-2-bromo-3-fluoro-5-(trideuteriomethoxy)benzene (2.44 g, 69%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.27 (m, 5H), 6.46 – 6.23 (m, 2H), 5.12 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.37 (d, J = 8.3 Hz).

Step 3: [2-Benzyloxy-6-fluoro-4-(trideuteriomethoxy)phenyl]boronic acid

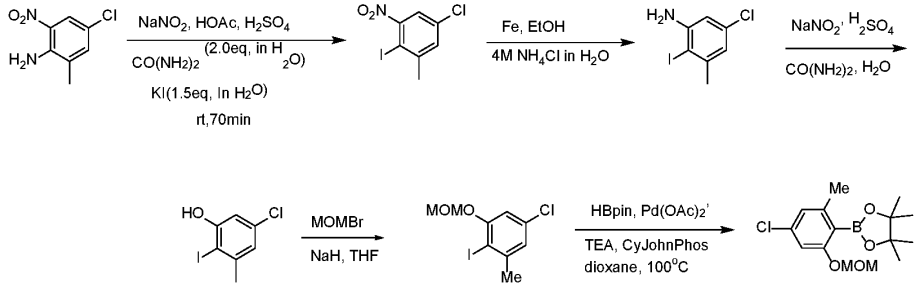
To an oven-dried 100-mL Schlenk flask equipped with a magnetic stir bar under argon atmosphere was added 1-benzyloxy-2-bromo-3-fluoro-5-(trideuteriomethoxy)benzene (3.96 g, 12.6 mmol) and dry tetrahydrofuran (42 mL, 3.33 L/mol). The resulting solution was cooled in a dry ice / isopropanol bath to an internal temperature of -70 °C. *n*-Butyllithium (5.6 mL, 2.7 M, 15.12 mmol, 1.20 equiv) was added dropwise, ensuring internal temperature did not rise above -65 °C. Once the addition was complete, the mixture was stirred for an additional 20 minutes at -78 °C. Tri-isopropyl borate (8.72 mL, 7.11 g, 37.8 mmol, 3.00 equiv) was added dropwise, again ensuring the internal temperature did not rise above -65 °C. Once the addition was complete, the reaction mixture was stirred for 2 hours at -78 °C and then allowed to warm to room temperature overnight. A large amount of white precipitate began to form as the reaction mixture warmed. After 20 h, the reaction mixture was cooled to 0 °C in an ice-water bath and quenched by the slow addition of 1 M aqueous HCl (20 mL). The heterogeneous mixture was then warmed to room temperature and stirred for 1 h. The layers were then separated, and the aqueous layer was extracted 3 times with ethyl acetate. Combined organic layers were washed with brine and dried over sodium sulfate, filtered, and concentrated on the rotavap (40 °C, 30 mmHg) to afford the crude product as a tan solid. Purification by column chromatography (0% to 50% EtOAc in hexanes) afforded [2-benzyloxy-6-fluoro-4-(trideuteriomethoxy)phenyl]boronic acid (1.75 g, 6.27 mmol, 50%) as an off-white solid that is best used immediately as it slowly decomposes in ambient conditions. MS m/z = 278.1 $[M–H]^-$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (br s, 2H), 7.62 – 7.21 (m, 5H), 6.55 – 6.24 (m, 2H), 5.08 (s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -103.94 (d, J = 10.5 Hz).

Intermediate 5g: 2-(2-(Benzyloxy)-6-fluoro-4-(methoxy-d3)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



The title compound was prepared in analogous manner according to the procedure of Intermediate 5g, using iodoethane in place of Iodomethane-d_3 in step 1. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.11 (s, 2H), 7.47 – 7.28 (m, 5H), 6.39 (d, J = 1.5 Hz, 1H), 6.30 (dd, J = 10.5, 1.8 Hz, 1H), 5.07 (s, 2H), 4.01 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H).

Intermediate 5h: 2-(4-Chloro-2-(methoxymethoxy)-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 5-Chloro-2-iodo-1-methyl-3-nitrobenzene

To a solution of 4-chloro-2-methyl-6-nitro-aniline (2.5 g, 13 mmol) in acetic acid (20 mL) was added a solution of sodium nitrite (1.46 g, 21.2 mmol) in H_2SO_4 (7.5 mL) dropwise. The mixture was allowed to stir at room temperature for 0.5 h. TLC (PE:EA = 10:1) showed the reaction was complete. Water (40 mL) and urea (1.46 g, 24.3 mmol) were added in and the mixture was stirred at room temperature for 10 min. A solution of potassium iodide (3.2 g, 19 mmol) in H_2O (20 mL) was added dropwise and the mixture was stirred at room temperature for 30 minutes and filtered. The filter cake was washed with water and dried in vacuum to get 5-chloro-2-iodo-1-methyl-3-nitrobenzene (4 g, 13.4 mmol, 98% Yield) as a brown solid.

Step 2. 5-Chloro-2-iodo-3-methylaniline

A stirred solution of ammonium chloride (2.15 g, 40.3 mmol) in water (10 mL) was added into a solution of 5-chloro-2-iodo-1-methyl-3-nitro-benzene (4 g, 13.4 mmol) in ethanol

(30 mL). The mixture was heated to 50 °C and Iron (3.76 g, 67.2 mmol) was added at one portion. The mixture was allowed to stir at reflux for 30 min and TLC (PE:EA = 10:1) showed the reaction was complete. The precipitate was filtered out. Ethanol was removed by evaporation and the aqueous solution was extracted with EtOAc. The organic layer was dried, filtered, and concentrated to get 5-chloro-2-iodo-3-methylaniline (3 g, 83.4% Yield) as a brown solid.

Step 3. 5-Chloro-2-iodo-3-methylphenol

To a solution of 5-chloro-2-iodo-3-methyl-aniline (2 g, 7.5 mmol) in water (50 mL) was added H_2SO_4 (0.5 M, 50 mL). The solution was heated to 80 °C. until all solid dissolved. Then the reaction was cooled to 0 °C. and sodium nitrite (774 mg, 11.2 mmol) was added in small portions. After 2 h at this temperature, urea (450 mg, 7.5 mmol) was added at 0 °C. The solution was allowed to warm up to room temperature and H_2SO_4 (0.5 M, 50 mL) was added. The reaction was refluxed for 30 min and cooled to room temperature. The solution was extracted with EtOAc and EtOH and the combined organic phases were dried over Na2SO4, purification by silica gel column (PE:EA=10:1), get 5-chloro-2-iodo-3-methylphenol (500 mg, 25% Yield) as red oil. MS *m/z* 266.9 $[M-H]^-$.

Step 4. 5-Chloro-2-iodo-1-(methoxymethoxy)-3-methylbenzene

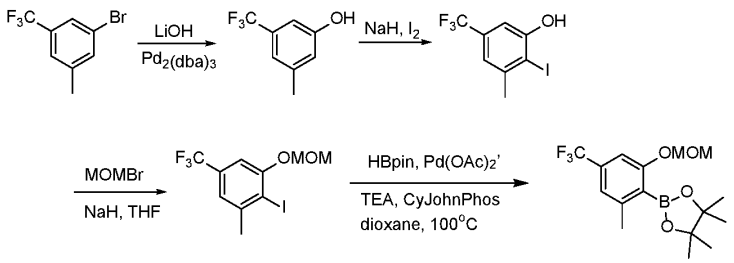
To a solution of 5-chloro-2-iodo-3-methylphenol (500 mg, 1.9 mmol) in THF (5 mL) was added NaH (72 mg, 3 mmol) at 0 °C. After that, the mixture was stirred at rt for 1h. Then MOMBr (375 mg, 3 mmol) was added in, and the reaction mixture was stirred at rt for another 0.5h. After that, water was added to quench the reaction. The mixture was extracted with EA. The organic layers were washed by H_2O and brine, then dried and concentrated under vacuum to give residue which was purified by SGC (PE/EtOAc = 10:1) to give 5-chloro-2-iodo-1-(methoxymethoxy)-3-methylbenzene (450 mg, 1.44 mmol, 80% yield) as red oil.

Step 5. 2-(4-Chloro-2-(methoxymethoxy)-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of 5-chloro-2-iodo-1-(methoxymethoxy)-3-methylbenzene (450 mg, 1.44 mmol) in 1,4-dioxane (6 ml) was added $Pd(OAc)_2$ (45 mg, 0.2 mmol), 2-(Dicyclohexylphosphino)biphenyl (121 mg, 0.35 mmol), TEA (1.01 g, 10 mmol) and HBPin (914 mg, 7.2 mmol). The mixture was stired at 80 degrees under nitrogen protection for 16h, monitored by LCMS. After that, the mixture was concentrated to give a residue which was purification by SGC (PE/EtOAc = 10:1) to give 2-(4-chloro-2-(methoxymethoxy)-6-

methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (169 mg, 0.54 mmol, 37.5% yield) as red oil.

Intermediate 5i: 2-(2-(Methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 3-Methyl-5-(trifluoromethyl)phenol

To a solution of 1-bromo-3-methyl-5-(trifluoromethyl)benzene (20 g, 83.7 mmol) in 1,4-Dioxane (200 ml) and H_2O (20 ml) were added $LiOH.H_2O$ (4.0 g, 167.3 mmol), $Pd_2(dba)_3$ (3.8 g, 4.2 mmol) and BippyPhos (1.7 g, 3.35 mmol). The reaction mixture was purged with Ar and stirred at 100 °C for 16 hours, monitored by TLC. After that, the mixture was cooled to RT, diluted with EtOAc (200 ml), washed with 1.5 M HCl and dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column to give 3-methyl-5-(trifluoromethyl)phenol (13 g, 73.4 mmol, 88% Yield). MS *m/z* 175.0 $[M-H]^+$.

Step 2. 2-Iodo-3-methyl-5-(trifluoromethyl)phenol

To a solution of 3-methyl-5-(trifluoromethyl)phenol (13 g, 73.4 mmol) in toluene (390 ml) was added NaH (3.54 g, 147.6 mmol) at 0 °C. The suspension was stirred at same temperature for 30 min. And then iodine (13.87 g, 55.1 mmol) was added slowly in portions and the mixture was stirred for 3 hours. After that, the mixture was diluted with water, acidified with 1 M HCl to pH 5 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column to give 2-iodo-3-methyl-5-(trifluoromethyl)phenol (6.6 g, 22.0 mmol, 30% Yield). MS *m/z* 300.9 $[M-H]^+$.

Step 3. 2-Iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene

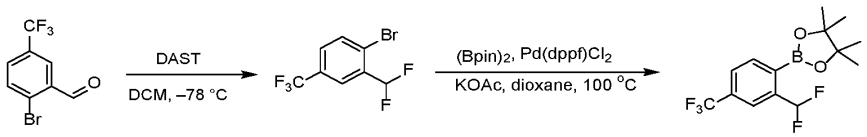
To a solution of 2-iodo-3-methyl-5-(trifluoromethyl)phenol (5.9 g, 20 mmol) in THF (60 ml) was added NaH (936 mg, 39 mmol) at 0 °C. The mixture was stirred at same temperature for 10 min, and then MOMBr (2.88 g, 23 mmol) was added in. This reaction solution was stirred at room temperature for 2 hours. After that, solvent was removed and the residue was purified by

silica gel column to give 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (4 g, 11.6 mmol, 59% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (s, 1H), 7.09 (s, 1H), 5.28 (s, 2H), 3.52 (s, 3H), 2.53 (s, 3H).

Step 4. 2-(2-(Methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of 2-iodo-1-(methoxymethoxy)-3-methyl-5-(trifluoromethyl)benzene (4 g, 11.6 mmol) in anhydrous 1, 4-dioxane (24 ml) were added pinacolborane (7.4 g, 58 mmol), biphenyl-2-yl-dicyclohexylphosphane (975 mg, 2.78 mmol), $Pd(OAc)_2$ (339 mg, 1.51 mmol)and TEA (8.2 g, 81.2 mmol). The mixture was purged with Ar and stirred at 80 °C for 16 hours. After that, the mixture was diluted with EtOAc and washed with saturated NH_4Cl, water and brine. The organic layer was dried over $NaSO_4$ and concentrated. The residue was purified by silica gel column to give 2-(2-(methoxymethoxy)-6-methyl-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 g, 8.7 mmol, 74.7% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 2H), 5.16 (s, 2H), 3.47 (s, 3H), 2.39 (s, 3H), 1.39 (s, 12H).

Intermediate 6a: 2-[2-(Difluoromethyl)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 1-Bromo-2-(difluoromethyl)-4-(trifluoromethyl)benzene

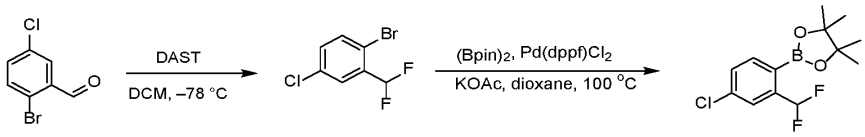
DAST (10 eq., 39.5 mmol) was added dropwise to a -78°C solution of 2-bromo-5-(trifluoromethyl)benzaldehyde (1 g, 3.9mmol) in DCM (5 mL, 78.0 mmol). The reaction was stirred for 15 min and then allowed to warm to room temperature. After 4 hours, TLC showed incomplete conversion, so the mixture was cooled again to -78°C and addition DAST (1 eq.,3.9 mmol) was added. The mixture was allowed to warm to rt. And was stirred overnight. The mixture was poured in ice and dilute NH_4OH and extracted 2x with DCM. The combined organic extracts were washed with brine and dried over sodium sulfate. Solvent evaporated in vacuum to give a residue which was purified with a short plug of silica to give the crude product 1-bromo-2-(difluoromethyl)-4-(trifluoromethyl)benzene (350 mg, 1.2mmol, 32.2% Yield) as colorless oil.

Step 2. 2-[2-(Difluoromethyl)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane

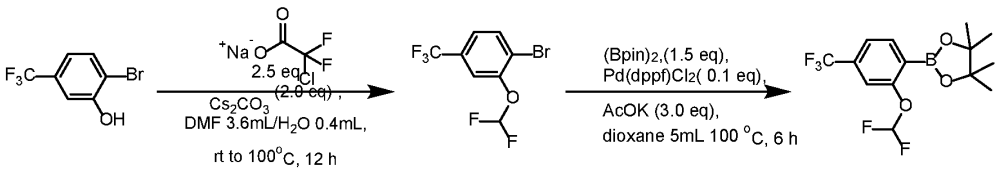
To a solution of 1-bromo-2-(difluoromethyl)-4-(trifluoromethyl)benzene (100 mg, 0.36 mmol) in 1,4-dioxane (2 mL) was added bis(pinacolato)diboron (1.5 eq., 0.5 mmol), potassium acetate (2 eq., 0.72 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii) (0.15 eq., 0.05 mmol). The mixture was stirred for 16 h at 100 °C for 16 hours under N_2 atmosphere, monitored by TLC and LCMS. After the reaction, the solution was removed under vacuum and the residue was purified by column chromatography (10-15% EA in PE) to afford 2-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30 mg, 0.09 mmol, 25.6% Yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.00 (d, J= 7.6 Hz, 1H),7.94 (d, J= 8.4 Hz, 1H),7.92 (s, 1H), 7.38 (t, J= 55.6 Hz, 1H),1.34 (s, 12H).

Intermediate 6b: 2-(4-Chloro-2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



The title compound was prepared in analogous manner according to the procedure of Intermediate 6a, using 2-bromo-5-chlorobenzaldehyde in place of 2-bromo-5-(trifluoromethyl)benzaldehyde in step 1. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.79 (d, J= 2.0 Hz, 1H), 7.68 –7.63 (m, 2H), 7.32(t, J= 55.6Hz, 1H), 1.32 (s, 12H).

Intermediate 7a: 2-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 1-Bromo-2-(difluoromethoxy)-4(trifluoromethyl)benzene

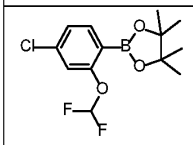
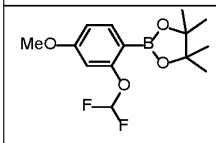
A mixture of 2-bromo-5-(trifluoromethyl)phenol (5.00 g, 20.7 mmol, 1.0 eq.), sodium 2-chloro-2,2-difluoroacetae (7.07 g, 51.9 mmol, 2.50 eq.) and cesium carbonate (11.5 g, 41.5 mmol, 2.0 eq.) in water (20 mL) and N,N-dimethylformamide (80 mL) was heated at 100 °C for

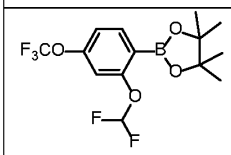
12 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. The reaction mixture was washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford 1-bromo-2-difluoromethoxy)-4(trifluoromethyl)benzene (2.8 g, 47% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.46 (t, J = 72.8 Hz, 1H), 7.5 (d, J = 8.4 Hz, 1H).

Step 2. 2-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

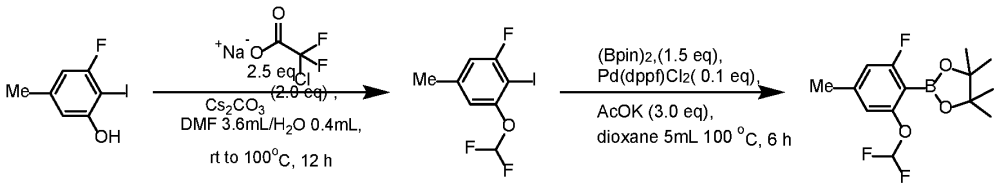
To a solution of 1-bromo-2-difluoromethoxy)-4(trifluoromethyl)benzene (2.80 g , 9.62 mmol) in 1,4-dioxane (30 mL) was added bis(pinacolato)diboron (36.6 g, 14.4 mmol, 1.50 eq.), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalldium(ll) (704 mg, 0.96 mmol, 0.1eq.), potassium acetate (2.82 g, 28.9 mmol, 3.0 eq.). The reaction mixture was heated at 100 °C for 16 hours under nitrogen. The reaction mixture was cooled to room temperature and filtered. The filtrate was diluted EA, washed with water and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with hexane to afford 2-(2-(difluoromethoxy)-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a white solid (1.70 g, 52% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.87 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H), 7.24 (t, J = 74.0 Hz, 1H), 1.31 (s, 12H).

The intermediates below were prepared according to the procedure of Intermediate 7a by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	MS *m/z* 304.5 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.68 (d, J= 8.4 Hz, 1H), 7.38 (d, J= 7.6 Hz, 1H), 7.30 (s, 1H), 7.16 (t, J= 74.4Hz, 1H), 1.30 (s, 12H).
	^{1}H NMR (400 MHz, DMSO–d6) δ 7.60 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 70.4 Hz, 1H), 6.86 (dd, J = 8.6, 2.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H), 1.27 (s, 12H).

Structure	Spectral Data
	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 8.2 Hz, 1H), 7.02 (s, 1H), 6.53 (t, J = 74.7 Hz, 1H), 1.26 (s, 12H).

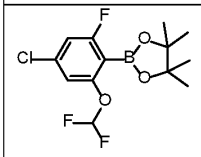
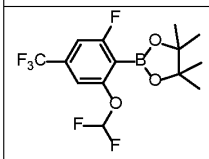
Intermediate 7b: 2-(2-(Difluoromethoxy)-6-fluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



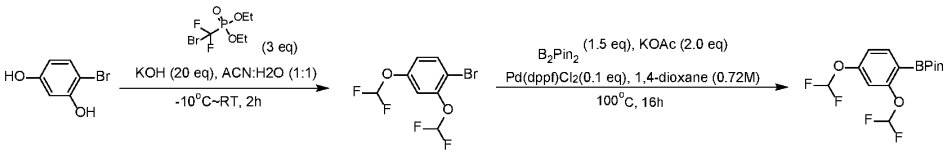
The starting material, 3-fluoro-2-iodo-5-methylphenol, was prepared in analogous manner according to the procedure of Intermediate 5d**,** step 1 to 3, using 3-fluoro-5-methylphenol in place of 3-chloro-5-fluorophenol in step 1.

The title compound was prepared in analogous manner according to the procedure of Intermediate 7a, using 3-fluoro-2-iodo-5-methylphenol in place of 2-bromo-5-(trifluoromethyl)phenol in step 1. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.92 (d, J = 10.0 Hz, 1H), 6.87 (s, 1H), 6.13 (t, J = 74.4 Hz, 1H), 2.34 (s, 3H), 1.29 (s, 12H).

The intermediates below were prepared according to the procedure of Intermediate 7b by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	^{1}H NMR (400 MHz, DMSO-d6) δ 7.36 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.27 (t, J = 73.6 Hz, 1H), 7.20 (s, 1H), 1.31 (s, 12H).
	^{1}H NMR (400 MHz, DMSO-d6) δ 7.60 (d, J = 8.4 Hz, 1H), 7.37 (t, 1H), 7.42 (s, 1H), 7.37 (t, J = 73.6 Hz, 1H), 1.32 (s, 12H).

Intermediate 7c: 2-(2,4-Bis(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



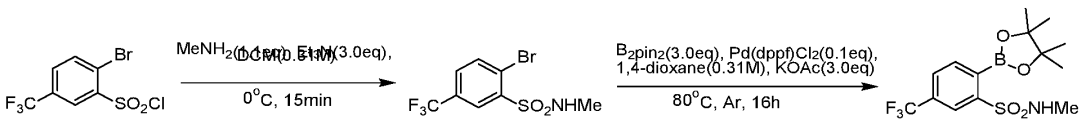
Step 1. 1-Bromo-2,4-bis(difluoromethoxy)benzene

To a solution of 4-bromobenzene-1,3-diol (10.0 g, 53.4 mmol, 1.0 eq.) in ACN/H_2O (1:1, 100 mL) was slowly added KOH (60.0 g, 1.07 mol, 20 eq.) at 0 °C. The mixture was stirred for 10 min and cooled to -10 °C. Diethyl (bromodifluoromethyl) phosphonate (42.70 g, 160.2 mmol, 3.0 eq.) was slowly added and the mixture was stirred for 10 min and warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (PE:EA = 0% ~ 5%) to give 1-bromo-2,4-bis(difluoromethoxy)benzene (3.30 g, 21.3% Yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ: 7.84 (d, J = 8.8 Hz, 1H), 7.38 (t, J = 72.0 Hz, 1H), 7.35 (t, J = 76.0 Hz, 1H), 7.26 (d, J = 2.8 Hz, 1H), 7.11 (dd, J = 8.8, 2.8 Hz, 1H).

Step 2. 2-(2,4-Bis(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of 1-bromo-2,4-bis(difluoromethoxy)benzene (3.30 g, 11.4 mmol, 1.0 eq.) in 1,4-dioxane was added KOAc (2.23 g, 22.8 mmol, 2.0 eq.), Pd(dppf)Cl_2 (0.830 g, 1.10 mmol, 0.1 eq.) and bis(pinacolato)diboron (4.34 g, 17.1 mmol, 1.5 eq.). The reaction mixture was stirred for 16 h at 100°C under N_2. The mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE: EA = 0% ~ 10%) to obtain 2-(2,4-bis(difluoromethoxy) phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 g, 6.0 mmol, 52% Yield) as yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 73.2 Hz, 1H), 7.12 (t, J = 74.4 Hz, 1H), 7.12 – 7.08 (m, 1H), 7.02 – 6.97 (m, 1H), 1.29 (s, 12H).

Intermediate 8: N-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzenesulfonamide



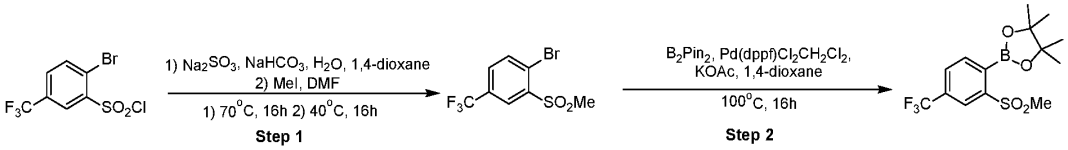
Step 1. 2-Bromo-N-methyl-5-(trifluoromethyl)benzenesulfonamide

To a solution of 2-bromo-5-(trifluoromethyl)benzenesulfonyl chloride (1.00 g, 3.09 mmol, 1.0 eq.) and triethylamine (942 mg, 9.27 mmol, 3.0 eq.) in DCM (10 mL) was added methylamine (392 mg, 27% in EtOH, 3.42 mmol, 1.1 eq.) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 15 min. Upon completion, the reaction mixture was diluted with DCM (80 mL) and washed with 1N HCl (50 mL), aqueous sat. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 0-20% EtOAc in hexanes to afford 2-bromo-N-methyl-5-(trifluoromethyl)benzenesulfonamide (930 mg, 2.92 mmol, 94.6% yield) as a white solid. ^{1}H NMR (400 Hz, DMSO-d6) δ: 8.17 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.95 (dd, J = 8.4, 2.0 Hz, 1H), 2.54 (s, 3H).

Step 2. N-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl) benzenesulfonamide

A mixture of 2-bromo-N-methyl-5-(trifluoromethyl) benzenesulfonamide (930 mg, 2.92 mmol, 1.0 eq.), bis(pinacolato)diboron (2.23 g, 8.78 mmol, 3.0 eq.), $Pd(dppf)Cl_2$-CH_2Cl_2 (239 mg, 0.292 mmol, 0.1 eq.) and potassium acetate (860 mg, 8.76 mmol, 3.0 eq.) in anhydrous 1,4-dioxane (9 mL) was stirred at 80 °C overnight under N_2 for 16 h. Upon completion, the reaction mixture was cooled to room temperature, filtered and rinsed with EtOAc (40 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexane to afford N-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzenesulfonamide (192 mg, 0.526 mmol, 18.0% yield) as a brown solid. ^{1}H NMR (400 Hz, DMSO-d6) δ: 8.21 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.6 Hz, 1H), 2.63 (d, J = 5.2 Hz, 3H), 1.42 (s, 12H).

Intermediate 9: 4,4,5,5-Tetramethyl-2-(2-(methylsulfonyl)-4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane



Step 1. 1-Bromo-2-(methylsulfonyl)-4-(trifluoromethyl)benzene

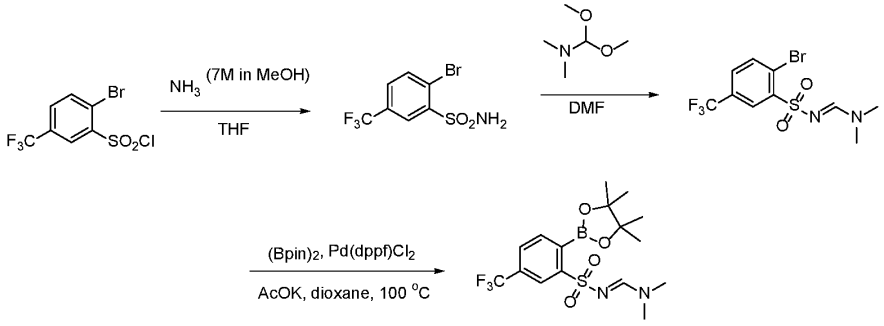
Sodium bicarbonate (779 mg, 9.27 mmol, 3.0 eq.) and sodium sulfite (779 mg, 6.18

mmol, 2.0 eq.) were heated in water (5 mL) at 70 °C for 5 min. A mixture of 2-bromo-5-(trifluoromethyl) benzenesulfonyl chloride (1.00 g, 3.09 mmol, 1.0 eq.) in 1,4-dioxane (10 mL) was added to the above mixture and stirred at 70 °C overnight. The solvents were removed in vacuo, then DMF (3 mL) and methyl iodide (483 mg, 3.43 mmol, 1.1 eq.) were added and reaction mixture was stirred at 4 0°C overnight. Upon completion, the reaction mixture was cooled to room temperature and diluted with water (30 mL). The mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to afford 1-bromo-2-(methylsulfonyl)-4-(trifluoromethyl) benzene as an orange oil (900 mg, 2.97 mmol, 96.1% yield). ^{1}H NMR (400 Hz, DMSO-d6) δ: 8.26 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.05 (dd, J = 8.2, 2.2 Hz, 1H), 3.48 (s, 3H).

Step 2. 4,4,5,5-Tetramethyl-2-(2-(methylsulfonyl)-4-(trifluoromethyl) phenyl)-1,3,2-dioxaborolane

A mixture of 1-bromo-2-(methylsulfonyl)-4-(trifluoromethyl) benzene (1.00 g, 3.30 mmol, 1.0 eq.), bis(pinacolato)diboron (2.51 g, 9.90 mmol, 3.0 eq.), Pd(dppf)Cl_2-CH_2Cl_2 (239 mg, 0.330 mmol, 0.1 eq.) and potassium acetate (970 mg, 9.90 mmol, 3.0 eq.) in anhydrous 1,4-dioxane (9 mL) was stirred at 100 °C overnight under N_2 for 16 h. Upon completion, the reaction mixture was cooled to room temperature, filtered and rinsed with EtOAc (40 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography eluting with 0-10% EtOAc in hexanes to afford 4,4,5,5-tetramethyl-2-(2-(methylsulfonyl)-4-(trifluoromethyl) phenyl)-1,3,2-dioxaborolane (858 mg, 2.45 mmol, 74.2% yield) as a brown solid. ^{1}H NMR (400 Hz, DMSO-d6) δ: 8.21 (s, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 3.36 (s, 3H), 1.35 (s, 12H).

Intermediate 10: (E)-N,N-Dimethyl-N'-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl)sulfonyl)formimidamide



Step 1. 2-Bromo-5-(trifluoromethyl)benzenesulfonamide

To ammonia (15ml, 105 mmol, 7 M in methanol) was added a THF (70 mL) solution of 2-bromo-5-(trifluoromethyl)benzenesulfonyl chloride (7 g, 21.6 mmol). This reaction mixture was stirred at RT for 3h, monitoring by LCMS. After that, solvent was removed and the residue was purification by SGC (PE: EA = 3: 1) to give 2-bromo-5-(trifluoromethyl)benzenesulfonamide (4.5 g, 15 mmol, 68% Yield) as colorless oil. MS *m/z* 301.8 $[M+H]^+$.

Step 2. (E)-N'-((2-Bromo-5-(trifluoromethyl)phenyl)sulfonyl)-N,N-dimethylformimidamide

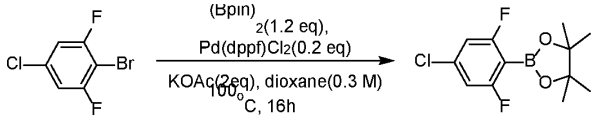
To a solution of 2-bromo-5-(trifluoromethyl)benzenesulfonamide (4.5 g, 15 mmol) in DMF (50 mL) was added N,N-dimethylformamide dimethyl acetal (2.6 g, 22 mmol). This mixture was stirred at RT for 0.5h, monitoring by LCMS. After that, the reaction mixture was diluted by water (100 mL) and extract by EtOAc (100 mL x 3). The combined organic was dried over Na_2SO_4, concentrated and purification by silica gel column (PE: EA= 3: 1) to get (E)-N'-((2-bromo-5-(trifluoromethyl)phenyl)sulfonyl)-N,N-dimethylformimidamide (3.9 g, 73% Yield) as white solid. MS *m/z* 360.9 $[M+H]^+$.

Step 3. (E)-N,N-Dimethyl-N'-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl)sulfonyl)formimidamide

A solution of (E)-N'-((2-bromo-5-(trifluoromethyl)phenyl)sulfonyl)-N,N-dimethylform-imidamide (3.9 g, 11mmol), bis(pinacolato)diboron (3.35 g, 13.2 mmol), potassium acetate (2200 mg, 22 mmol), and $Pd(dppf)Cl_2$ (800 mg, 1.1 mmol) in 1,4-dioxane (40mL) was stirred at 90 °C under N_2 for 16h, monitoring by LCMS. After reaction, solvent was removed and the

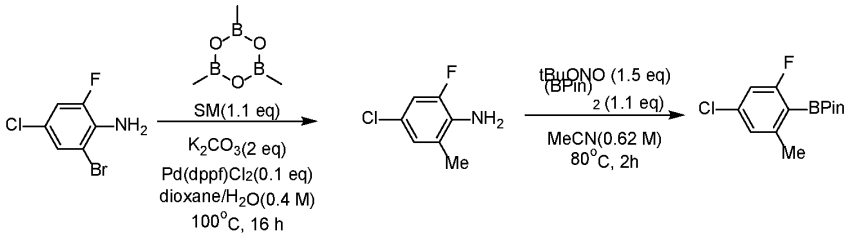
residue was purified by silica gel column (PE: EA=3: 1) to get (E)-N,N-dimethyl-N'-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl)sulfonyl)formimidamide (300 mg, 9% Yield) as yellow oil. MS *m/z* 407.3 $[M+H]^+$.

Intermediate 11a: 2-(4-Chloro-2,6-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a solution of 2-bromo-5-chloro-1,3-difluorobenzene (200 mg, 0.880 mmol, 1.0 eq.) in 1,4-dioxane (3 mL, 0.3 M) was added bis(pinacolato)diboron (246 mg, 0.970 mmol, 1.1 eq.), 1,1'-bis(diphenyphosphino)ferrocene (25 mg, 0.044 mmol, 0.05 eq.), $Pd(dppf)Cl_2$ (32 mg, 0.044 mmol, 0.05 eq.) and KOAc (259 mg, 2.64 mmol, 3.0 eq.). The reaction mixture was stirred for 8 h at 80 °C under N_2. The mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (PE: EA = 50:1 to 20:1) to obtain 2-(4-chloro-2,6-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (220 mg, 0.80 mmol, 91% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ 7.64 (d, J = 6.8 Hz, 2H), 1.23 (s, 12H).

Intermediate 11b: 2-(4-Chloro-2-fluoro-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 4-Chloro-2-fluoro-6-methylaniline

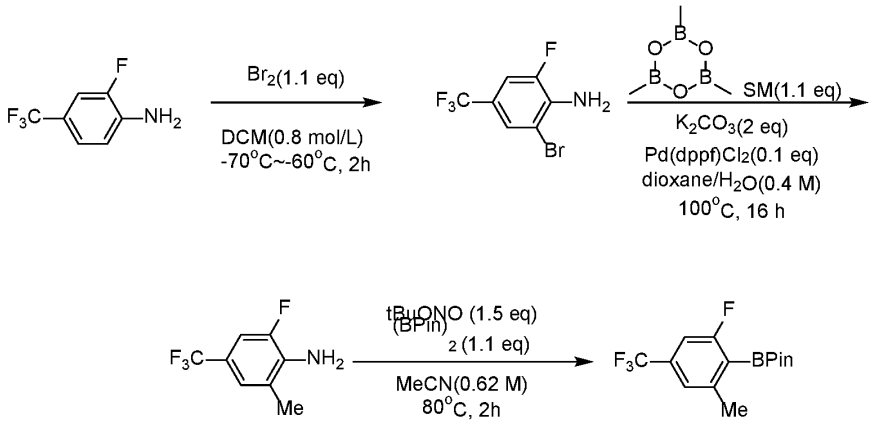
To a solution of 2-bromo-4-chloro-6-fluoroaniline (5.00 g, 22.3 mmol, 1.0 eq.) in 1,4-dioxane/H_2O (5:1, 50 mL) were added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.07 g, 24.5 mmol, 1.1 eq.), K_2CO_3 (6.15 g, 44.6 mmol, 2.0 eq.) and $Pd(dppf)Cl_2$ (1.63 g, 2.2 mmol, 0.1 eq.). The reaction mixture was stirred for 16 h at 100 °C under N_2. The mixture was poured into water

(100 mL) and extracted with DCM (100 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was concentrated in vacuum to give 4-chloro-2-fluoro-6-methylaniline (1.50 g, crude) as yellow oil which was used directly to the next step without further purification. MS *m/z* 160.2 $[M+H]^+$,

Step 2. 2-(4-Chloro-2-fluoro-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of crude 4-chloro-2-fluoro-6-methylaniline (0.25 g) from above step in MeCN (2.5 mL) was added tert-butyl nitrite (0.24 g, 2.30 mmol, 1.5 eq.) and bis(pinacolato)diboron (0.45 g, 1.80 mmol, 1.1 eq.). The reaction mixture was stirred for 2 h at 80 °C. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (PE:EA = 20:1) to obtain 2-(4-chloro-2-fluoro-6-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.5 g, containing bis(pinacolato)diboron) as yellow oil, which was used in the next step directly without further purification. ^1H NMR (400 MHz, DMSO-d6) δ 6.67 (d, J = 1.8 Hz, 1H), 6.65 – 6.56 (m, 1H), 2.38 (s, 3H), 1.31 (s, 12H).

Intermediate 11c: 2-(2-Fluoro-6-methyl-4-(trifluoromethyl) phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



Step 1. 2-Bromo-6-fluoro-4-(trifluoromethyl)aniline

To a solution of 1-(tert-butyl) 2-methyl (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (7.00 g, 39.1 mmol, 1.0 eq.) in DCM (50 mL, 0.8 M) was added Br_2 (6.87 g, 43.0 mmol, 1.1 eq.)

slowly at -70 °C ~ -60 °C. The mixture was stirred at -70 °C~-60 °C for 2 h, then diluted with DCM, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to give crude 2-bromo-6-fluoro-4-(trifluoromethyl)aniline as yellow oil, which was used in the next step without further purification. MS *m/z* 256.1, 257.9 $[M-H]^-$.

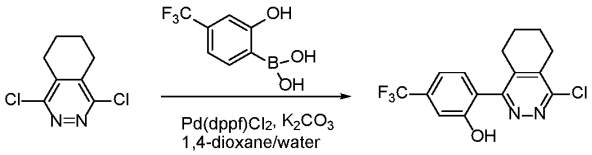
Step 2. 2-Fluoro-6-methyl-4-(trifluoromethyl)aniline

To a solution of crude 2-bromo-6-fluoro-4-(trifluoromethyl) aniline (2.0 g) from above step in 1,4-dioxane/H_2O (5:1, 50 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.07 g, 8.50 mmol, 1.1 eq.), K_2CO_3 (2.10 g, 15.5 mmol, 2.0 eq.) and $Pd(dppf)Cl_2$ (0.57 g, 0.800 mmol, 0.1 eq.). The reaction mixture was stirred for 16 h at 100 °C. The mixture was diluted with water (30 mL) and extracted with DCM (30 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was concentrated in vacuo to give 2-fluoro-6-methyl-4-(trifluoromethyl) aniline (840 mg, crude) as yellow oil, which was used in the next step without further purification.

Step 3. 2-(2-Fluoro-6-methyl-4-(trifluoromethyl) phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a solution of crude 2-fluoro-6-methyl-4-(trifluoromethyl) aniline (0.84 g) in MeCN (10 mL) was added tert-butyl nitrite (0.67 g, 6.5 mmol, 1.5 eq.) and bis(pinacolato)diboron (1.20 g, 4.70 mmol, 1.1 eq.). The reaction mixture was stirred for 2 h at 80°C, then diluted with water (50 mL) and extracted with DCM (80 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give crude methyl (2S,4S)-4-methylsulfonyloxy-1-trityl-pyrrolidine-2-carboxylateas yellow oil, which was used in the next step without further purification. ^1H NMR (400 MHz, DMSO-d6) δ: 7.43 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 2.46 (s, 3H), 1.33 (s, 12H).

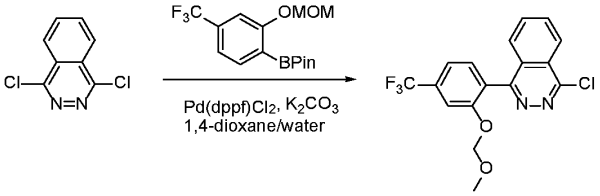
Intermediate 12: 2-(4-Chloro-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol



A mixture of 1,4-dichloro-5,6,7,8-tetrahydro-phthalazine (2.95 g, 14.5 mmol), [2-hydroxy-4-(trifluoromethyl)phenyl] boronic acid (3 g, 14.5 mmol), $Pd(dppf)Cl_2$ (1.07 g, 1.45 mmol) and K_2CO_3 (4.02 g, 29.1 mmol) in 1,4-dioxane (30 mL) and water (3 mL) was stirred at

100 °C for 16 h under N_2 atmosphere. After that, the mixture was diluted with water (20 ml), extracted with EtOAc (50 ml x 3), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column (DCM:MeOH~10%) to give 2-(4-chloro-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol (2 g, 42% yield) as a red solid. MS *m/z* 329.0, 331.0 $[M+H]^+$.

Intermediate 13: 1-Chloro-4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)phthalazine

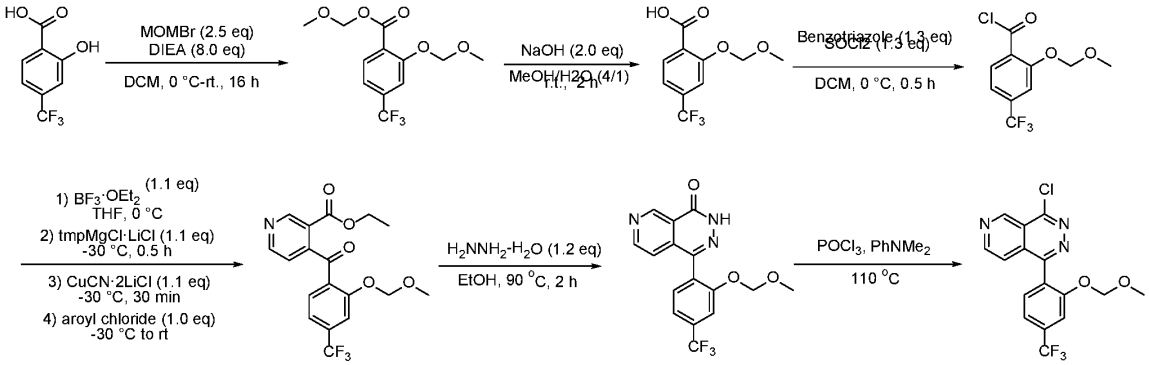


The title compound was prepared in analogous manner according to the procedure of Intermediate 12, using 1,4-dichlorophthalazine in place of 1,4-dichloro-5,6,7,8-tetrahydro-phthalazine. MS *m/z* 369.4, 371.0 $[M+H]^+$.

Intermediate 14a: 1-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4(3H)-one

and

Intermediate 14b: 4-Chloro-1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazine



Step 1. Methoxymethyl 2-(methoxymethoxy)-4-(trifluoromethyl)benzoate

To a mixture of 2-hydroxy-4-(trifluoromethyl)benzoic acid (150 g, 727 mmol) in DCM (1.2 L) was added DIPEA (635 mL, 3640 mmol). The mixture was stirred at 0 °C and MOMBr (173 mL, 2185 mmol) was added dropwise. The resulting mixture was stirred at rt for 16 h. TLC

(Petroleum ether/EtOAc 7:1) indicated the reaction was completed. The mixture was washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to provide title product (211 g, 99% yield) as light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 5.46 (s, 2H), 5.42 (s, 2H), 3.51 (s, 3H), 3.45 (s, 3H).

Step 2. 2-(Methoxymethoxy)-4-(trifluoromethyl)benzoic acid

To a stirred solution of methoxymethyl 2-(methoxymethoxy)-4-(trifluoromethyl)benzoate (500 g, 1.7 mol) in MeOH (6 L) and water (1.5 L) was added NaOH (140 g, 3.5 mol) in portions at 0 °C. The resulting mixture was stirred at rt for 2 h. After concentration to remove MeOH, the aqueous phase was acidified to pH = 3 with HCl (1M). The precipitates were collected by filtration, washed with water and dried under vacuum to provide 2-(methoxymethoxy)-4-(trifluoromethyl)benzoic acid (400 g, 94 % Yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.33 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 5.36 (s, 2H), 3.42 (s, 3H).

Step 3. 2-(Methoxymethoxy)-4-(trifluoromethyl)benzoyl chloride

A stock solution was prepared by dissolving 1H-indazole (38.7 g, 328 mmol), thionyl chloride (38.4 g, 323 mmol) in 200 mL DCM. Reaction was carried out by adding the stock solution intermittently to a stirred solution of 2-(methoxymethoxy)-4-(trifluoromethyl)benzoic acid (65 g, 259.8 mmol) in DCM (1 L). Before addition was complete, benzotriazole hydrochloride started precipitating out as a white solid. The mixture was stirred for another 0.5 h. After filtration, the filtrate was stirred with $MgSO_4$ $7H_2O$ (50 g) to destroy excess thionyl chloride. The white solid was filtered off and the filtrate was concentrated to give crude product (62 g, 88.8% Yield), which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.50 (s, 1H), 7.36 (dd, *J* = 8.3, 0.7 Hz, 1H), 5.33 (s, 2H), 3.54 (s, 3H).

Step 4. Ethyl 4-(2-(methoxymethoxy)-4-(trifluoromethyl)benzoyl)nicotinate

Ethyl pyridine-3-carboxylate (130 g, 860 mmol,) was dissolved in THF (950 mL) and boron trifluoride diethyl ether (135 g, 951 mmol) was added slowly at – 40 °C. After stirring for 0.5 h, 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex solution (950 mL, 950 mmol, 1.0 mol/L in THF) was added slowly and the mixture was stirred for 30 min. Then fresh prepared copper cyanide lithium chloride complex solution in THF (CuCN (89.3 g,

997 mmol) and LiCl (82.84 g, 1954 mmol) in THF (950 mL) was stirred at 25°C for 16 h) was added. After stirring for 0.5 h, 2-(methoxymethoxy)-4-(trifluoromethyl)benzoyl chloride (260 g, 968 mmol,) in THF was added slowly and stirred for another 0.5 h. The mixture was warmed to rt and quenched with aqueous ammonium chloride solution and pH was adjusted to ~8-9 with additional ammonia. The mixture was extracted with EA. The EA phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was purified by silica gel column (PE: EA =5:1 to 1:1 as eluent) to provide ethyl 4-(2-(methoxymethoxy)-4-(trifluoromethyl)benzoyl)nicotinate (158 g, 47.9% Yield) as yellow oil. MS *m/z* 384.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.90 (d, *J* = 5.0 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.43 (s, 1H), 5.00 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.02 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H).

Step 5. 1-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4(3H)-one (14a)

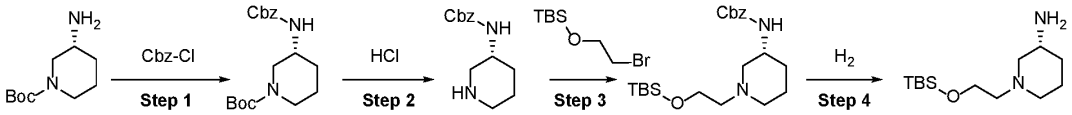
To a solution of ethyl ethyl 4-(2-(methoxymethoxy)-4-(trifluoromethyl)benzoyl)nicotinate (50 g, 130 mmol) in EtOH (500 mL) was added hydrazine (7.8 g, 156 mmol) and the mixture was stirred at 90 °C for 2 h. After cooling to rt, the precipitate was filtered and the filter cake was washed with EtOH and dried under vacuum to obtain 1-(2-(methoxymethoxy)-4-(trifluoromethyl) phenyl)pyrido[3,4-d]pyridazin-4(3H)-one (36 g, 78.5% Yield) as white solid. MS *m/z* 352.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.52 (s, 1H), 8.96 (d, *J* = 5.5 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 5.5 Hz, 1H), 5.24 (d, *J* = 12.6 Hz, 2H), 3.21 (s, 3H).

Step 6. 4-Chloro-1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazine (14b)

A mixture of 1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4(3H)-one (50 g, 142 mmol) and N,N-dimethylaniline (68.7 g, 568 mmol) in $POCl_3$ (434 g, 2.84 mol) was stirred for 30 min at 110 °C. After cooling to rt, the mixture was concentrated to remove excess of $POCl_3$, the residue was adjusted to pH = 7-8 with TEA and purified by silica gel column chromatography (EA: PE= 1:3) to provide 4-chloro-1-(2-(methoxymethoxy)-4-(trifluoromethyl) phenyl)pyrido[3,4-d]pyridazine (22 g, 41.8% yield) as light yellow solid. MS *m/z* 370.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.80 (d, *J* = 0.9 Hz, 1H), 9.13 (d, *J* = 5.7 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.67 (s, 1H), 7.65 – 7.60 (m, 2H), 5.22 (d, *J* = 20.0 Hz, 2H),

3.16 (s, 3H).

Intermediate 15a: (3R)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine



Step 1. tert-Butyl (3R)-3-(benzyloxycarbonylamino)piperidine-1-carboxylate

To a solution of tert-butyl (R)-3-aminopiperidine-1-carboxylate (30 g, 0.15 mol) in 330 ml THF and 83 ml water was added Na_2CO_3(43 g, 0.31 mol). And then Cbz-Cl (34, 0.199 mol) was added dropwised into the mixture with ice bath, monitored by TLC. After 5 hours, the reaction was extracted with EA, dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified via flash chromatography (PE: EA = 4:1) to give tert-butyl (3R)-3-(benzyloxycarbonylamino) piperidine-1-carboxylate (35 g, 84% Yield). MS *m/z* 235.1 [M-Boc+H]$^+$

Step 2. Benzyl N-[(3R)-3-piperidyl]carbamate

A solution of tert-butyl (3R)-3-(benzyloxycarbonylamino)piperidine-1-carboxylate (35g, 0.104 mol**)** in 450 mL DCM was added HCl (350 mL, 4M in 1,4-dioxane), monitored by TLC. After 2 h, the solvent was removed in vacuo to give crude benzyl N-[(3R)-3-piperidyl]carbamate (25 g, 0.106 mol, 100% yield) which was used for next step without purification. MS *m/z* 234.1 [M+H]$^+$.

Step 3. Benzyl N-[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]carbamate

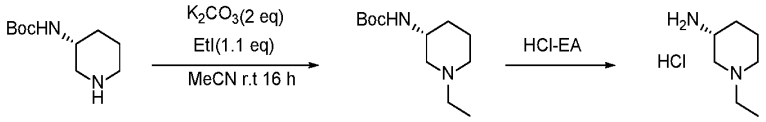
To a solution of benzyl N-[(3R)-3-piperidyl]carbamate (25 g, 0.106 mol) in CH_3CN (680 mL) was added Cs_2CO_3 (175 g, 0.537 mol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (40 g, 0.167 mol). The reaction was stirred 90 °C for 16 h. After reaction, the mixture was filtered and the solvent was removed in vacuo, then crude product was purified via flash chromatography to give the product benzyl N-[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]carbamate (22.5 g, 0.057 mol, 53% Yield). MS *m/z* 393.2 [M+H]$^+$.

Step 4. (3R)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine

To a solution of benzyl N-[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]carbamate (22.5 g, 0.057 mol) in MeOH (60 mL) was added Pd/C (4.5 g, 20%). The

system was evacuated and refilled with hydrogen. Then the mixture stirred at R.T overnight. After reaction, the mixture was filtered, the solvent was removed in vacuo and the crude product was purified via flash chromatography to give the product (3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine (12 g, 81% Yield). MS *m/z* 259.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, J = 6.6 Hz, 2H), 2.85 – 2.74 (m, 2H), 2.67 – 2.58 (m, 1H), 2.46 (t, J = 6.4 Hz, 2H), 2.11 – 2.01 (m, 1H), 1.94 – 1.83 (m, 1H), 1.83 – 1.71 (m, 4H), 1.68 – 1.58 (m, 1H), 1.56 – 1.43 (m, 1H), 1.09 – 0.96 (m, 1H), 0.88 – 0.79 (m, 9H), 0.04 – (-)0.04 (m, 6H).

Intermediate 15b: (R)-1-Ethylpiperidin-3-amine hydrochloride



Step 1. tert-Butyl (R)-(1-ethylpiperidin-3-yl)carbamate

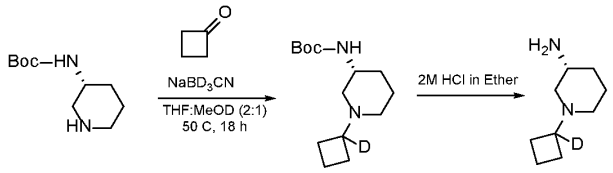
To a solution of tert-butyl (R)-piperidin-3-ylcarbamate (4 g, 20 mmol) in MeCN (40 mL) was added K_2CO_3 (2.76 g, 20 mmol) and MeI (3.12 g, 20 mmol) at 20°C under N_2. The mixture was stirred at 20°C for 16 hours. TLC showed the reaction was completed. The reaction mixture was poured into water (100 mL) and extracted with EA (100 mL x 2). The combined organic layers were washed with brine (100 mL x 2). dried over Na_2SO_4, filtered and concentrated. Purified by column (DCM:MeOH=0-10%) to give tert-butyl (R)-(1-ethylpiperidin-3-yl)carbamate (3.6 g, 15.8 mmol, 78.9% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d6) δ 6.65 (d, *J* = 7.8 Hz, 1H), 3.32 (s, 1H), 2.70 (dd, *J* = 41.0, 9.7 Hz, 2H), 2.29 (q, *J* = 7.1 Hz, 2H), 1.83 – 1.53 (m, 4H), 1.48 – 1.40 (m, 1H), 1.37 (s, 9H), 1.11 (qd, *J* = 11.8, 3.7 Hz, 1H), 0.96 (t, *J* = 7.2 Hz, 3H).

Step 2. (R)-1-Ethylpiperidin-3-amine hydrochloride

To a solution of tert-butyl (R)-(1-ethylpiperidin-3-yl)carbamate (3.6 g, 15.8 mmol) in MeOH (10 mL) was added HCl (30 mL, 3 M in EA) at RT. The mixture was stirred at 20°C for 16 hours. TLC showed the reaction was completed. The reaction mixture was concentrated to give(R)-1-ethylpiperidin-3-amine hydrochloride (3.03 g, 15.0 mmol, 95.0% yield) as yellow oil. MS *m/z* 129.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 3.83 – 3.59 (m, 3H), 3.36 – 3.30 (m, 2H), 3.18 – 2.96 (m, 2H), 2.25 (d, *J* = 12.7 Hz, 1H), 2.15 (d, *J* = 14.9 Hz, 1H), 2.07 – 1.92 (m,

1H), 1.76-1.72 (m, 1H), 1.43 (t, *J* = 7.3 Hz, 3H).

Intermediate 15c: (R)-1-(Cyclobutyl-1-d)piperidin-3-amine



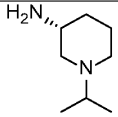
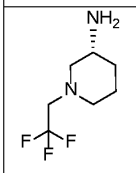
Step 1: *tert*-Butyl (R)-(1-(cyclobutyl-1-d)piperidin-3-yl)carbamate

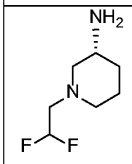
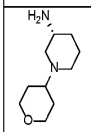
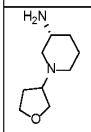
A mixture of *tert*-butyl (*R*)-piperidin-3-ylcarbamate (200 mg, 1.0 mmol, 1.0 eq.), sodium cyanoborodeuteride (200 mg, 3.0 mmol, 3.0 eq.) was dissolved in 1.2 mL of THF: MeOD (5:1) mixture followed by the addition of cyclobutanone (150 mg, 2.1 mmol). The reaction mixture was then stirred at 50 ^{o}C for 18 h. The crude reaction mixture was allowed to cool to room temperature and diluted with DCM (10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (2 mLx3) followed by brine and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was used for the following step without further purification. MS *m/z* 256.2 $[M+H]^+$.

Step-2: (R)-1-(Cyclobutyl-1-d)piperidin-3-amine

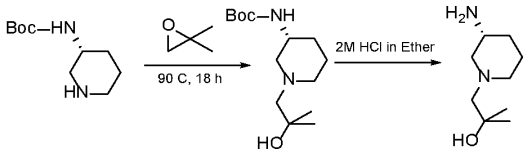
The crude compound from previous step was dissolved in DCM (5 mL) and then 2M HCl solution in ether (3 mL) was added slowly at rt while the mixture was vigorously stirred. The reaction mixture was stirred at rt overnight and then concentrated *in vacuo* to afford a yellow solid (138 mg) of HCl salt. The amine was used without further purification. MS *m/z* 156.2 $[M+H]^+$.

The intermediates below were prepared according to the procedure of Intermediate 15b or c by substituting the appropriate starting materials, reagents and reaction conditions.

Structure	Spectral Data
	MS *m/z* 243.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 3.83–3.72 (m, 1H), 3.71–3.61 (m, 2H), 3.56–3.48 (m, 1H), 3.15 –3.03 (m, 2H), 2.30–2.19 (m, 1H), 2.18–2.10 (m, 1H), 2.09–1.97 (m, 1H), 1.81–1.66 (m, 1H), 1.43 (d, *J* = 6.7 Hz, 6H).
	MS *m/z* 183.2 $[M+H]^+$; ^{1}H NMR(400 MHz, CD_3OD) δ 4.00 (q, J = 9.3 Hz, 2H), 3.65 (ddd, J = 22.7, 13.2, 8.3 Hz, 2H), 3.39 (d, J = 12.2 Hz, 1H), 3.26 – 3.06 (m, 2H), 2.09 (dtd, J = 23.9, 8.6, 4.2 Hz, 2H), 2.01 – 1.85 (m, 1H), 1.72 (dtd, J = 13.8, 10.1, 3.7 Hz, 1H).

Structure	Spectral Data
	^{1}H NMR(400 MHz, CD_3OD) δ 6.48 (tt, J = 53.5, 3.7 Hz, 1H), 3.84 – 3.64 (m, 4H), 3.59 (d, J = 11.9 Hz, 1H), 3.22 (dt, J = 12.2, 7.1 Hz, 2H), 2.15 (dtd, J = 15.1, 7.9, 3.8 Hz, 2H), 2.07 – 1.93 (m, 1H), 1.71 (ddd, J = 15.2, 11.9, 3.8 Hz, 1H).
	MS *m/z* 185.2[M+H]$^+$
	MS *m/z* 171.2[M+H]$^+$

Intermediate 15d: (*R*)-1-(3-Aminopiperidin-1-yl)-2-methylpropan-2-ol



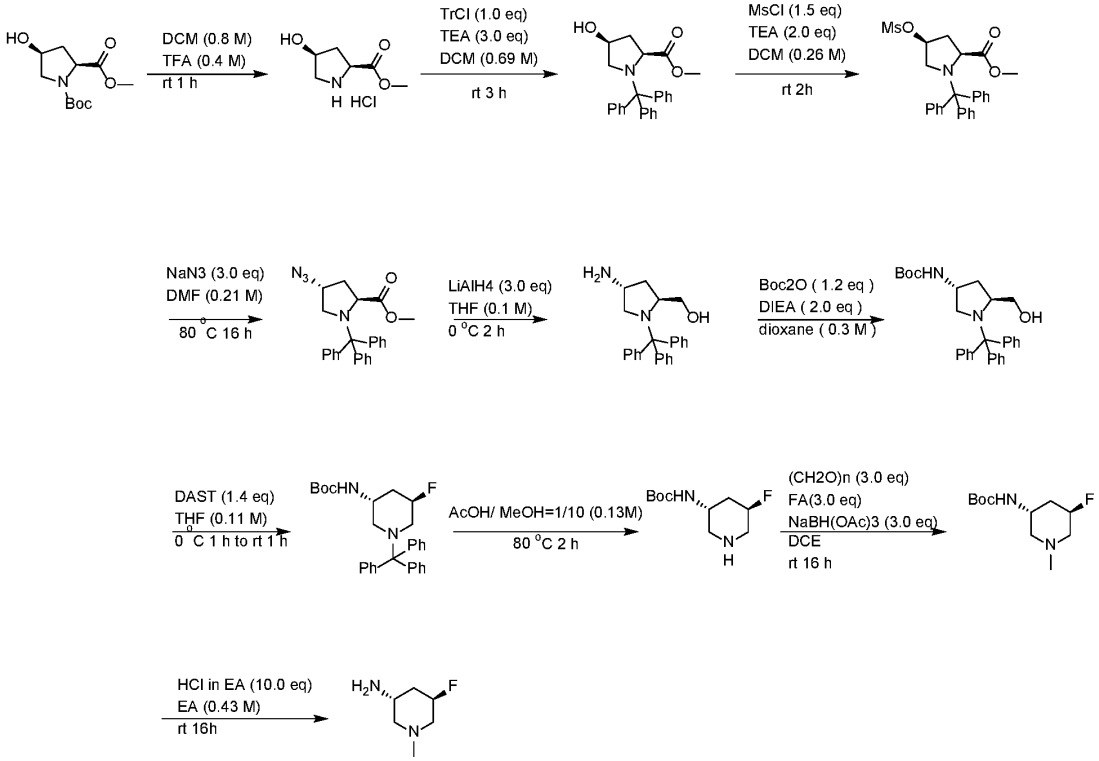
Step-1: *tert*-Butyl (R)-(1-(2-hydroxy-2-methylpropyl)piperidin-3-yl)carbamate

A mixture of *tert*-butyl (R)-piperidin-3-ylcarbamate (700 mg, 3.5 mmol, 1.0 eq.), and 2,2-dimethyloxirane (800 mg, 11.1 mmol, 3.2 eq.) was stirred at 90 C for 18 h. The crude reaction mixture was allowed to cool to room temperature and diluted with DCM (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (4 mLx2) followed by brine and water. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was used then for the following step. MS *m/z* 273.3 [M+H]$^+$.

Step-2: (*R*)-1-(3-Aminopiperidin-1-yl)-2-methylpropan-2-ol

The crude compound from previous step was dissolved in DCM (5 mL) and then 2M HCl solution in ether (10 mL) was added slowly at rt while the mixture was vigorously stirred. The reaction mixture was stirred at rt for overnight and concentrated *in vacuo* to afford a light brown solid (520 mg) of HCl salt. The amine was used without further purification. MS *m/z* 173.2 [M+H]$^+$.

Intermediate 16a: (3R,5R)-5-Fluoro-1-methylpiperidin-3-amine hydrochloride



Step 1. Methyl (2S,4S)-4-hydroxypyrrolidine-2-carboxylate

1-(tert-Butyl) 2-methyl (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (10.0 g, 40.8 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. TFA (10 mL, 132.3 mmol) was slowly added and the mixture was warmed to room temperature and stirred for 1 h. The mixture was concentrated in vacuo to give crude methyl (2S,4S)-4-hydroxypyrrolidine-2-carboxylate as yellow oil, which was used to next step without further purification. MS *m/z* 146.1 $[M+H]^+$.

Step 2. Methyl (2S,4S)-4-hydroxy-1-tritylpyrrolidine-2-carboxylate

To a solution of crude methyl (2S,4S)-4-hydroxypyrrolidine-2-carboxylate from above step in DCM (50 mL) was added TEA (12.4 g, 123 mmol) and Ph_3CCl (11.4 g, 40.9 mmol,). The reaction mixture was stirred for 2 h at rt. The mixture was poured into water and extracted with DCM (30 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (PE: EA =10:1 to 5:1) to obtain methyl (2S,4S)-4-hydroxy-1-trityl-pyrrolidine-2-carboxylate (7.60 g, 20.0 mmol, 48% Yield for two steps) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m,

6H), 7.32 – 7.23 (m, 6H), 7.21 – 7.13 (m, 3H), 3.92 – 3.80 (m, 3H), 3.65 (s, 3H), 3.46 (d, *J* = 11.5 Hz, 1H), 2.80 (dd, *J* = 11.5, 3.8 Hz, 1H), 1.62 (d, *J* = 13.8 Hz, 1H), 1.38 – 1.11 (m, 1H).

Step 3. Methyl (2S,4S)-4-((methylsulfonyl)oxy)-1-tritylpyrrolidine-2-carboxylate

To a solution of methyl (2S,4S)-4-hydroxy-1-trityl-pyrrolidine-2-carboxylate (10.0 g, 25.8 mmol) in DCM (100 mL) was added TEA (7.90 g, 78.0 mmol) and MsCl (4.50 g, 39.0 mmol). The reaction mixture was stirred for 2 h at rt. The mixture was diluted with water and extracted with DCM (80 mL x 2). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give crude methyl (2S,4S)-4-methylsulfonyloxy-1-trityl-pyrrolidine-2-carboxylateas yellow oil, which was used in the next step directly.

Step 4. Methyl (2S,4R)-4-azido-1-tritylpyrrolidine-2-carboxylate

To a solution of methyl (2S,4S)-4-methylsulfonyloxy-1-trityl-pyrrolidine-2-carboxylate from above step in DMF (140 mL) was added sodium azide (7.80 g, 120 mmol). The reaction mixture was stirred for 16 h at 80 °C. The reaction mixture was diluted with water and extracted with EA (3 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (PE: EA = 0% ~ 10%) to give methyl (2S,4R)-4-azido-1-trityl-pyrrolidine-2-carboxylate (8.00 g, 19.4 mmol, 64.5% Yield for two steps) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 6H), 7.33 – 7.24 (m, 6H), 7.18 (t, *J* = 7.3 Hz, 3H), 4.20 – 4.06 (m, 1H), 3.91 (d, *J* = 8.9 Hz, 1H), 3.72 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.63 (s, 3H), 2.63 (dd, *J* = 10.3, 7.8 Hz, 1H), 1.90 – 1.79 (m, 1H), 0.94 – 0.88 (m, 1H).

Step 5. ((2S,4R)-4-Amino-1-tritylpyrrolidin-2-yl)methanol

To a stirred suspension of LiAlH4 (2.20 g, 58.0 mmol) in THF (80 mL) at 0 °C was added a solution of a solution of methyl (2S,4R)-4-azido-1-trityl-pyrrolidine-2-carboxylate (8.00 g, 19.4 mmol) in THF (10 mL). After the addition was completed, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with water (2.5 mL), 15% NaOH solution (2.5 mL) and water (6 mL). After stirring for 0.5 h, the mixture was dried over Na2SO4, filtered and concentrated to give crude product [(2S,4R)-4-amino-1-trityl-pyrrolidin-2-yl]methanol as yellow oil (7.00 g, 19.5 mmol, >99% Yield), which was used to the next step without purification.

Step 6. tert-Butyl ((3R,5S)-5-(hydroxymethyl)-1-tritylpyrrolidin-3-yl)carbamate

To a solution of [(2S,4R)-4-amino-1-trityl-pyrrolidin-2-yl]methanol (7.00 g, 19.5 mmol)

in 1,4-dioxane (70 mL) was added TEA (3.90 g, 39.0 mmol) and $(Boc)_2O$ (5.10 g, 23.0 mmol). The mixture was stirred for 2 h at rt, then diluted with water and extracted with EA (3 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (PE: EA = 20:1) to give tert-butyl N-[(3R,5S)-5-(hydroxymethyl)-1-trityl-pyrrolidin-3-yl]carbamate (8.00 g, 17.4 mmol, 89.3% Yield) as colorless oil. MS *m/z* 459.3 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.50 (m, 6H), 7.33 – 7.23 (m, 7H), 7.18 (t, *J* = 7.3 Hz, 3H), 4.27 – 4.18 (m, 1H), 3.77 – 3.64 (m, 2H), 3.58 – 3.51 (m, 1H), 3.50 – 3.32 (m, 2H), 2.60 – 2.48 (m, 1H), 2.03 – 1.94 (m, 1H), 1.90 – 1.81 (m, 1H), 1.36 (s, 9H).

Step 7. tert-Butyl ((3R,5R)-5-fluoro-1-tritylpiperidin-3-yl)carbamate

DAST (2.80 mL, 21.0 mmol) was added dropwise to a stirred solution of tert-butyl N-[(3R,5S)-5-(hydroxymethyl)-1-trityl-pyrrolidin-3-yl]carbamate (6.80 g, 15.0 mmol) in THF (70 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and 1 h at RT, then cooled to 0°C again. A saturated aqueous solution of Na_2CO_3 was added to adjust pH to 12. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 40 mL). The organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, PE/EtOAc= 20/1) to afford tert-butyl N-[(3R,5R)-5-fluoro-1-trityl-3-piperidyl]carbamate (3.90 g, 8.50 mmol 57% Yield) as a white solid. MS *m/z* 483.3 $[M+Na]^+$,

Step 8. tert-Butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate

To a solution of tert-butyl N-[(3R,5R)-5-fluoro-1-trityl-3-piperidyl]carbamate (3.90 g, 8.50 mmol) in MeOH (80 mL) was added AcOH (8 mL, 139.6 mmol). The mixture was stirred for 2 h at 80 °C, then concentrated under reduced pressure. The residue was diluted with EA (20 mL) and H_2O (20 mL). The mixture was acidified with aqueous HCl till pH = 2-3 and extracted with EA (10 mL x 2). The aqueous layers were basified with aqueous K_2CO_3 till pH = 9-10 and extracted with DCM (50 mL x 3). The DCM layers were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide tert-butyl N-[(3R,5R)-5-fluoro-3-piperidyl]carbamate (1.60 g, 7.30 mmol 87% Yield) as a white solid. MS *m/z* 219.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ 6.61 (s, 1H), 4.77 (d, *J* = 48.5 Hz, 1H), 3.60 (br s, 1H), 2.96 – 2.82 (m, 2H), 2.77 – 2.62 (m, 1H), 2.43 – 2.33 (m, 1H), 2.09 – 1.97 (m, 1H), 1.78 – 1.55 (m, 1H), 1.39 (s, 9H)

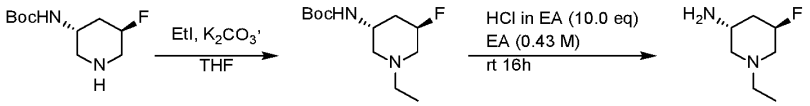
Step 9. tert-Butyl ((3R,5R)-5-fluoro-1-methylpiperidin-3-yl)carbamate

To a solution of tert-butyl N-[(3R,5R)-5-fluoro-3-piperidyl]carbamate (1.60 g, 7.30 mmol) in DCE (20 mL) was added formic acid (1.20 g, 26.0 mmol,) and (HCHO)n (0.75 g, 25 mmol) and stirred for 1 h at rt. To the mixture was added $NaBH(OAc)_3$ (5.4 g, 25.0 mmol) and stirred for 16 h at rt. The reaction mixture was quenched with water, basified with aqueous K_2CO_3 solution and extracted with DCM. The organic phase was combined and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EA = 3/1) to afford tert-butyl N-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]carbamate (1.00 g, 4.30 mmol, 59.0% Yield) as a white solid. MS *m/z* 233.1 $[M+H]^+$,

Step 10. (3R,5R)-5-Fluoro-1-methylpiperidin-3-amine hydrogen chloride

To a solution of tert-butyl N-[(3R,5R)-5-fluoro-1-methyl-3-piperidyl]carbamate (1.00 g, 4.30 mmol) in EA (10 mL) was added HCl in 1,4-dioxane (14 mL, 56 mmol, 4 mol/L). The resulting mixture was stirred at room temperature for 2 h, then filtered and the solid was wash with EA (2 mL) and dried under vacuum to give (3R,5R)-5-fluoro-1-methyl-piperidin-3-amine (750 mg, 5.67 mmol, 75% Yield) as a white solid. MS *m/z* 133.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 11.18 (d, J = 3.6 Hz, 1H), 8.94 (s, 3H), 5.25 (d, J = 44.4 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.56 – 3.50 (m, 1H), 3.41 – 3.27 (m, 1H), 3.13 (t, J = 11.2 Hz, 1H), 2.85 (s, 3H), 2.47 – 2.41 (m, 1H), 2.01 – 1.83 (m, 1H).

Intermediate 16b: (3R,5R)-5-Fluoro-1-ethylpiperidin-3-amine hydrochloride



The starting material, tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate, was prepared as the procedure of Intermediate 16a step 1 to 8.

The title compound was prepared in analogous manner according to the procedure of Intermediate 15b, using tert-butyl ((3R,5R)-5-fluoropiperidin-3-yl)carbamate in place of tert-butyl (R)-piperidin-3-ylcarbamate in step 1. MS *m/z* 147.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ : 11.02 (s, 1H), 8.94 (s, 3H), 5.27 (d, J = 44.8 Hz, 1H), 3.74 - 3.62 (m, 3H), 3.32 - 3.22 (m, 3H), 3.09 - 3.05 (m, 1H), 2.48-2.43 (m, 1H), 2.06-1.89 (m, 1H), 1.28 – 1.25 (t, J = 14.0 Hz, 3H).

Intermediate 17: tert-Butyl 2-(aminomethyl)azetidine-1-carboxylate



Step 1. tert-Butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate

To a solution of tert-butyl 2-(hydroxymethyl)azetidine-1-carboxylate (1000 mg, 5.34 mmol) and triethylamine (820 mg, 8.10 mmol) in dichloromethane (10 mL, 156.0 mmol) at 0°C was added methanesulfonyl chloride (800 mg, 6.98 mmol). This mixture was stirred at r.t for 2 hour, monitored by TLC and LCMS. The mixture was then poured into H_2O, extracted with CH_2Cl_2 (30*2ml). The combined organic was dried over Na_2SO_4 and concentrated under vacuum to get crude tert-butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate (900 mg, 64% Yield) which was used in the next reaction directly. MS *m/z* 166.2 $[M\text{-Boc}+H]^+$.

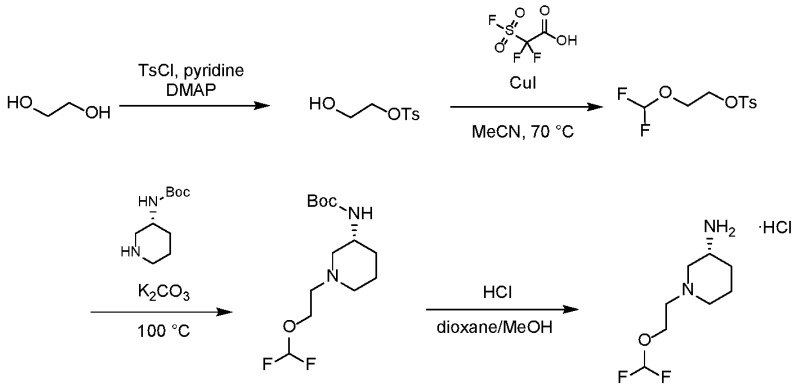
Step 2. tert-Butyl 2-(azidomethyl)azetidine-1-carboxylate

To a solution of tert-butyl 2-(methylsulfonyloxymethyl)azetidine-1-carboxylate (800 mg, 3.02mmol) in N,N-dimethylformamide (10 mL, 129 mmol) was added sodium azide (300 mg, 4.6 mmol) successively. This mixture was stirred at 60 °C overnight, monitored by TLC and LCMS. The mixture was poured into H_2O, extracted with EA (2 x 30 ml). The combined organic was dried over Na_2SO_4 and concentrated under vacuum to give crude tert-butyl 2-(azidomethyl)azetidine-1-carboxylate (700 mg, 84% Yield) which was used in next reaction directly. MS *m/z* 235.3 $[M+Na]^+$.

Step 3. tert-Butyl 2-(aminomethyl)azetidine-1-carboxylate

To a solution of tert-butyl 2-(azidomethyl)azetidine-1-carboxylate (700 mg, 3.30 mmol) in methanol (10 mL, 247 mmol) was added Pd/C (70 mg, 0.066 mmol). Then the mixture was stirred overnight at RT under H2 atmosphere, monitored by TLC and LCMS. After reaction, Pd/C was filtrated out and the filtrate was concentrated under vacuum to give crude tert-butyl 2-(aminomethyl)azetidine-1-carboxylate (500 mg, 81% Yield) which was used in the next reaction directly. MS *m/z* 187.1 $[M+H]^+$.

Intermediate 18: (*R*)-1-(2-(Difluoromethoxy)ethyl)piperidin-3-amine hydrochloride



Step 1: 2-Hydroxyethyl 4-methylbenzenesulfonate

A mixture of ethylene glycol (2.5 g, 40 mmol), TsCl (1.90 g, 10 mmol), pyridine (1.1 g, 12 mmol) and DMAP (12 mg, 0.1 mmol) was stirred at rt for 18 h. The reaction mixture was partitioned between DCM (20 mL) and 0.5 M hydrochloric acid. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 60%) gave a colorless oil (1.32 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.25 Hz, 2 H), 7.37 (d, J = 8.13 Hz, 2 H), 4.15 (t, J = 4.50 Hz, 2 H), 3.83 (t, J = 4.63 Hz, 2 H), 2.46 (s, 3 H), 2.00 (br s, 1 H).

Step 2. 2-(Difluoromethoxy)ethyl 4-methylbenzenesulfonate

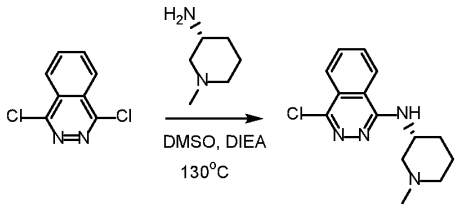
To a stirred solution of 2-hydroxyethyl 4-methylbenzenesulfonate (1.70 g, 7.86 mmol) in MeCN (13 mL) was added copper (I) iodide (0.300 g, 1.57 mmol). The resulting mixture was stirred at 70 °C and treated with 2,2-difluoro-2-fluorosulfonyl-acetic acid (2.80 g, 15.7 mmol) as a solution in MeCN (10 mL) dropwise over a period of 25 min. The resulting mixture was treated with anhydrous Na_2SO_4 (small scoop) and stirring continued for 1.5 h. The mixture was then cooled to rt, diluted with Et_2O and washed with brine, a 1:1 mixture of brine: water (2x), and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0-25%) gave a pale yellow oil (0.759 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.25 Hz, 2 H), 7.49 (d, J = 8.13 Hz, 2 H), 6.65 (t, J = 75.04 Hz, 1 H), 4.22 – 4.16 (m, 2 H), 4.04 – 3.98 (m, 2 H), 2.43 (s, 3 H)

Step 3 and 4: **(*R*)-1-(2-(Difluoromethoxy)ethyl)piperidin-3-amine hydrochloride**

t-Butyl *N*-[(3*R*)-3-piperidyl]carbamate (0.500 g, 2.50 mmol) in DMF (10 mL) was added 2-(difluoromethoxy)ethyl 4-methylbenzenesulfonate (0.764 g, 2.87 mmol) and K_2CO_3 (0.690 g,

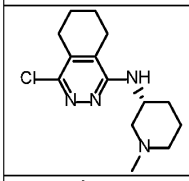
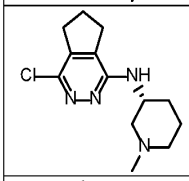
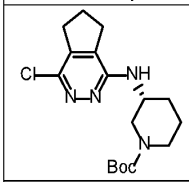
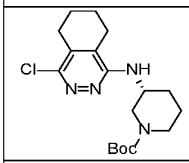
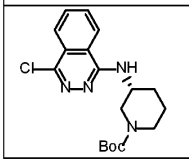
4.99 mmol). The mixture was stirred at 100 °C for 2 h. The reaction was diluted with DCM/iPrOH (9:1) and washed with water, brine, dried over Na_2SO_4, filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 5 to 60%) gave a pale yellow oil (0.709 g). The oil was dissolved in MeOH (2.0 mL), treated with HCl/dioxane (4.0 M, 3 mL) and stirred for 4 h. The mixture was concentrated, resuspended in ether and filtered to give a white solid (0.371 g, 67%). ^{1}H NMR (400 MHz, D_2O) δ 6.45 (t, J = 73.6 Hz, 1 H), 4.26 (t, J = 5.2 Hz, 2 H), 3.81 (d, J = 11.2 Hz, 1 H), 3.67 -3.58 (m, 2 H), 3.55 (t, J = 4.8 Hz, 2 H), 3.15 - 3.02 (m, 2 H), 2.21 (d, J = 12.4 Hz, 1 H), 2.11 (d, J = 15.2 Hz, 1 H), 1.90 – 1.79 (m, 1 H), 1.70 -1.60 (m, 1 H).

Intermediate 19a: (R)-4-Chloro-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

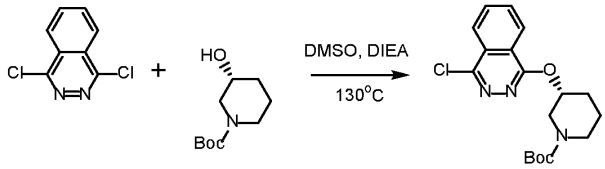


To a solution of 1,4-dichlorophthalazine (200 mg, 1.0048 mmol) in 1-methyl-2-pyrrolidinone (3 mL) was added (3R)-1-methylpiperidin-3-amine (1.5 eq., 1.5 mmol) and N,N-diisopropylethylamine (3.0 eq., 3.0 mmol). The resulting mixture was heated to 100 °C and kept stirring at that temperature for 12 h. Aqueous workup followed by purification by C18 reverse phase EZ-Prep using formic acid as the additive gave 4-chloro-*N*-[(3*R*)-1-methyl-3-piperidyl]phthalazin-1-amine (60 mg, 21.6% Yield) as a yellow solid. MS *m/z* 277.0, 279.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.47-8.44 (d, 1H), 8.08-8.04 (m, 1H), 8.02-7.96 (m, 2H), 7.27(d, J = 7.6 Hz, 1H), 4.35-4.28 (m, 1H), 3.05(d, J= 8.0Hz, 1H), 2.72(d, J= 10.8 Hz, 1H), 2.22 (s, 3H), 1.97-1.94 (m, 3H), 1.77-1.72 (m, 1H), 1.65-1.54(m, 1H), 1.49-1.39 (m, 1H).

The compounds below were prepared according to the procedure of Example Intermediate 19a by substituting the appropriate starting materials (commercially available), reagents and reaction conditions.

Structure	Spectral Data
	MS *m/z* 281.2, 283.2 $[M+H]^+$.
	^1H NMR (400 MHz, DMSO-d6) δ 6.17 (d, J=8.0 Hz, 1 H), 4.16-4.08 (m, 1H), 2.92 (d, J=7.6 Hz, 1 H), 2.84 (t, J=7.6 Hz, 2 H), 2.77 (t, J=7.6Hz, 2 H), 2.65 (d, J=10.8 Hz, 1 H), 2.18 (s,3H), 2.10-2.02 (m,2H), 1.93-1.84 (m,3H), 1.71-1.66 (m, 1 H), 1.59-1.54 (m, 1 H), 1.37-1.27 (m, 1 H)
	MS *m/z* 353 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.30 – 4.26 (m, 1H), 3.64 – 3.55 (m, 3H), 3.30-3.27 (s, 1H), 2.97 (t, J = 7.6 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.24 – 2.16 (m, 2H), 1.92 – 1.90 (m ,2H), 1.72 – 1.69 (m, 1H), 1.57 – 1.55 (m, 1H), 1.42 (s, 9H).
	MS *m/z* 367.2 $[M+H]^+$.
	MS *m/z* 363.1, 365.0 $[M+H]^+$.

Intermediate 19b: tert-Butyl (R)-3-((4-chlorophthalazin-1-yl)oxy)piperidine-1-carboxylate

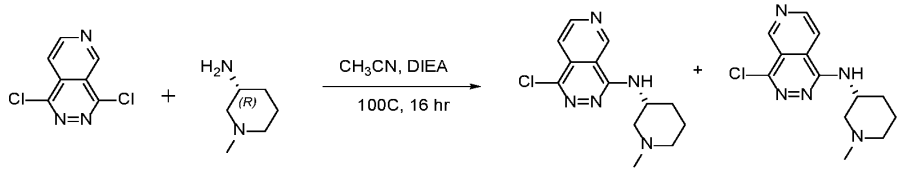


To a solution of 1,4-dichlorophthalazine (200 mg, 1.0048 mmol) in N,N-dimethylformamide (2 mL) was added tert-butyl (3*R*)-3-hydroxypiperidine-1-carboxylate (1.2 equiv., 1.21 mmol) and sodium tert-butoxide (1 mL, 2 M in THF). The resulted mixture was bubbled with argon and then was added (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (0.05 equiv., 0.050 mmol). The reaction mixture was kept bubbling argon for another 5 min. The reaction vessel was sealed, the reaction was heated to 100°C for 5 h. UPLC showed completion of the reaction, the reaction mixture was filtered through a pad of Celite. The filtrate was worked up and concentrated. The

residue was purified over silica with methanol and dichloromethane (0 to 30% gradient) to give tert-butyl (3*R*)-3-(4-chlorophthalazin-1-yl)oxypiperidine-1-carboxylate (300 mg, 82% Yield). MS *m/z* 364.0 $[M+H]^+$.

Intermediate 20a: (R)-1-Chloro-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine and

Intermediate 20b: (R)-4-Chloro-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-1-amine



To the solution of 1,4-dichloropyrido[3,4-d]pyridazine (28 g, 140 mmol) in acetonitrile (824 mL, 0.17M) was added (3R)-1-methylpiperidin-3-amine dihydrochloride (39.3 g, 210 mmol, 1.5 eq) and DIPEA (54.3 g, 420 mmol, 3 eq). Then the mixture was stirred at 100 ℃ for 16 h under N_2. After the reaction, precipitate was filtered under reduced pressure to give a light-yellow solid salt (20 g) and the filtrate was concentrated in vacuum to give a brown residue. The light-yellow solid salt was solved in aqueous saturated sodium carbonate solution and the pH value was adjusted to 9 by aqueous saturated sodium carbonate solution. This aqueous solution was extracted with dichloromethane (150 ml x 2). The combined organics were dried over sodium sulfate, concentrated and purified by silica gel column chromatography using FlashColum （8% MeOH/DCM) to get (R)-1-chloro-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine (13 g, 33% Yield) as a light yellow solid. MS *m/z* 278 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.80 (s, 1H), 9.05 (d, *J* = 5.6 Hz, 1H), 7.85 (d, *J* = 5.6 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 4.55 – 4.24 (m, 1H), 3.05 (d, *J* = 7.4 Hz, 1H), 2.72 (d, *J* = 10.9 Hz, 1H), 2.21 (s, 3H), 2.04 – 1.82 (m, 3H), 1.82 – 1.69 (m, 1H), 1.67 – 1.51 (m, 1H), 1.43 (m, 1H).

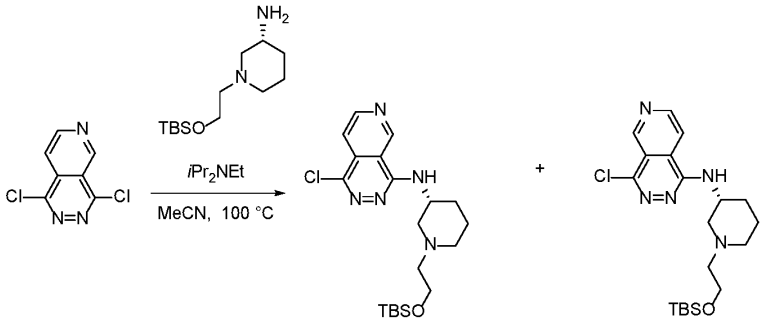
The brown residue was dissolved in DCM(300 ml), washed with water (100 ml x 3), dried over sodium sulfate, concentrated and purified by silica gel column chromatography using FlashColum (8% MeOH/DCM) to give a mixture of region-isomers which were further purified on SFC to provide another regio-isomer, (R)-4-chloro-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-1-amine, as clean product. MS *m/z* 278 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.40 (s, 1H), 9.09 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 4.34 –

4.29 (m, 1H), 3.03 (d, *J* = 7.4 Hz, 1H), 2.71 (d, *J* = 10.9 Hz, 1H), 2.21 (s, 3H), 2.0 – 1.9 (m, 3H), 1.74 – 1.73 (m, 1H), 1.60 – 1.57 (m, 1H), 1.44 – 1.40 (m, 1H).

Intermediate 20c: (*R*)- -(1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)piperidin-3-yl)-1-chloropyrido[3,4-*d*]pyridazin-4-amine

and

Intermediate 20d: (*R*)-*N*-(1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)piperidin-3-yl)-4-chloropyrido[3,4-*d*]pyridazin-1-amine



To a solution of 1,4-dichloropyrido[3,4-d]pyridazine (1.75 g, 8.75 mmol) and (3*R*)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine (Intermediate 15a, 2.49 g, 9.62 mmol) in MeCN (48 mL) was added *i*Pr$_2$NEt (4.6 mL, 26.2 mmol). The solution was sparged with Ar for 10 min and then heated to 100 °C for 6 h. The reaction was concentrated and purified by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) to give an orange gum containing a ~3:1 mixture of compound (3*R*)-1-[2-[tert-butyl(dimethyl)silyl]- oxyethyl]piperidin-3-amine and its regioisomer (2.89 g, 78%), which were separated by SFC.

(3*R*)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine: MS *m/z* 422.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.79 (s, 1H), 9.05 (d, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 5.5 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 4.40 – 4.27 (m, 1H), 3.69 (t, *J* = 6.1 Hz, 2H), 3.20 – 3.11 (m, 1H), 2.89 – 2.78 (m, 1H), 2.48 – 2.41 (m, 2H), 2.09 – 1.95 (m, 3H), 1.80 – 1.66 (m, 1H), 1.64 – 1.50 (m, 1H), 1.49 – 1.38 (m, 1H), 0.82 (s, 9H), 0.03 (s, 6H).

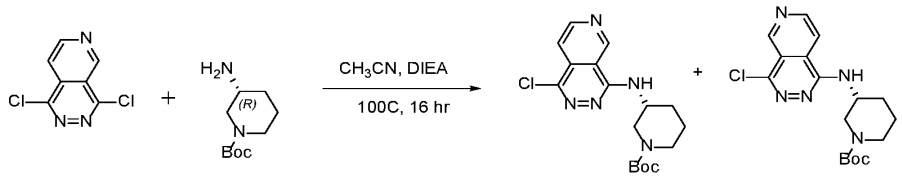
(*R*)-*N*-(1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)piperidin-3-yl)-4-chloropyrido[3,4-*d*]pyridazin-1-amine: MS *m/z* 422.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.40 (s, 1H), 9.09 (d, *J* = 5.6 Hz, 1H), 8.33 (d, *J* = 5.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.18 (m, 1H), 3.69 (t, *J* = 6.1 Hz, 2H), 3.19 – 3.07 (m, 1H), 2.84 (d, *J* = 11.3 Hz, 1H), 2.49 – 2.43 (m, 2H), 2.10

– 1.91 (m, 3H), 1.79 – 1.65 (m, 1H), 1.62 – 1.36 (m, 2H), 0.82 (s, 9H), 0.03 (s, 6H).

Intermediate 20e: tert-Butyl (R)-3-((1-chloropyrido[3,4-d]pyridazin-4-yl)amino)piperidine-1-carboxylate

and

Intermediate 20f: tert-Butyl (R)-3-((4-chloropyrido[3,4-d]pyridazin-1-yl)amino)piperidine-1-carboxylate



The title compounds were prepared in analogous manner according to the procedure of Intermediate 20c and Intermediate 20d, using tert-butyl (R)-3-aminopiperidine-1-carboxylate in place of (3*R*)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine.

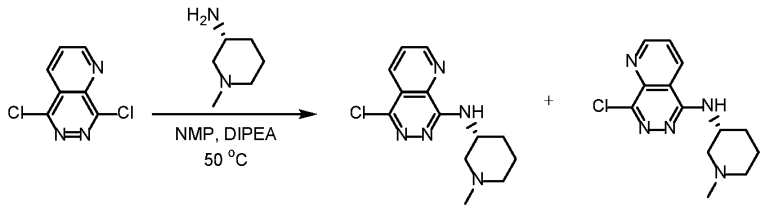
tert-Butyl (R)-3-((1-chloropyrido[3,4-d]pyridazin-4-yl)amino)piperidine-1-carboxylate. ^{1}H NMR (acetone-d6) δ: 9.49 (s, 1H), 9.06 (d, J = 5.5 Hz, 1H), 8.14 (br s, 1H), 6.88 (br s, 1H), 4.30-4.45 (m, 1H), 4.00-4.25 (m, 1H), 3.72-3.85 (m, 1H), 3.00-3.40 (m, 2H), 2.15-2.25 (m, 1H), 1.70-1.93 (m, 2H), 1.55-1.67 (m, 1H), 1.30-1.50 (br s, 9H).

tert-Butyl (R)-3-((4-chloropyrido[3,4-d]pyridazin-1-yl)amino)piperidine-1-carboxylate. ^{1}H NMR (acetone-d6) δ: 9.69 (s, 1H), 9.08 (d, J = 5.5 Hz, 1H), 7.93 (d, J = 5.5 Hz, 1H), 7.10 (br s, 1H), 4.30-4.45 (m, 1H), 4.03-4.25 (m, 1H), 3.79-3.90 (m, 1H), 3.00-3.40 (m, 2H), 2.15-2.25 (m, 1H), 1.70-1.97 (m, 2H), 1.50-1.64 (m, 1H), 1.30-1.50 (br s, 9H).

Intermediate 21a: (*R*)-5-Chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-8-amine

and

Intermediate 21b: (*R*)-8-Chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-5-amine



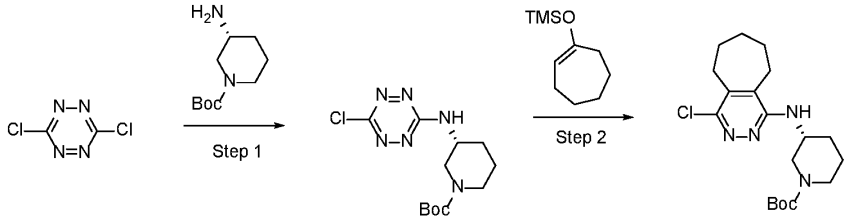
A solution of (3*R*)-1-methylpiperidin-3-amine (1.14 g, 10 mmol, 2 eq) in NMP (2 mL)

was added to a solution of 5,8-dichloropyrido[2,3-*d*]pyridazine (1.00 g, 5.0 mmol, 1 eq) in NMP (18 mL) followed by the addition of *N*,*N*-diisopropylethylamine (2.0 mL, 11.5 mmol, 2.3 eq) and was stirred at 50 ^{0}C for 1 day. After completion, the reaction was diluted with EtOAc and NaHCO3 (sat. aq.). The product was extracted several times with EtOAc (100 mL x 5) from 1M K_2CO_3 (200 mL) and the combined organic extracts were washed with a small amount of 1M K_2CO_3 (2 X 25 mL), washed with 25 mL brine and were dried over Na_2SO_3 and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 1:99 to 25:75 MeOH:DCM to afford (*R*)-5-chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-8-amine (497 mg, 36%) and (*R*)-8-chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-5-amine (643 mg, 46%), respectively.

(*R*)-5-Chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-8-amine. MS *m/z* 278.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.20 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 8.6 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 4.40 – 4.25 (m, 1H), 2.73 – 2.59 (m, 1H), 2.42 – 2.25 (m, 3H), 2.21 (s, 3H), 1.81 – 1.62 (m, 3H), 1.59 – 1.48 (m, 1H).

(*R*)-8-Chloro-*N*-(1-methylpiperidin-3-yl)pyrido[2,3-*d*]pyridazin-5-amine. MS *m/z* 278.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.21 (d, *J* = 4.4 Hz, 1H), 8.89 (d, *J* = 1.3 Hz, 1H), 8.03 – 7.92 (m, 1H), 7.54 – 7.39 (m, 1H), 4.37 – 4.21 (m, 1H), 3.07 – 2.95 (m, 1H), 2.77 – 2.60 (m, 1H), 2.19 (s, 3H), 2.03 – 1.82 (m, 3H), 1.80 – 1.68 (m, 1H), 1.64 – 1.50 (m, 1H), 1.49 – 1.32 (m, 1H).

Intermediate 22: tert-Butyl (R)-3-((4-chloro-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate



Step 1: tert-Butyl (R)-3-((6-chloro-1,2,4,5-tetrazin-3-yl)amino)piperidine-1-carboxylate

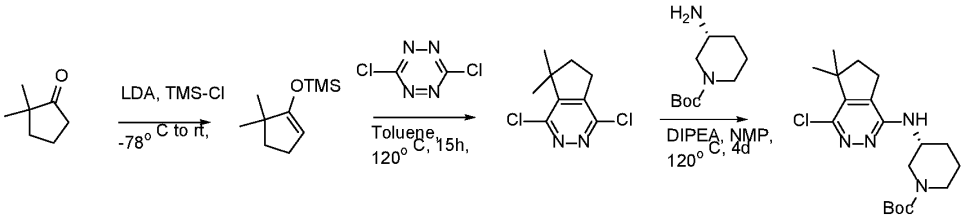
3,6-Dichloro-1,2,4,5-tetrazine (100 mg, 0.66 mmol) and tert-butyl (R)-3-aminopiperidine-1-carboxylate (138 mg, 0.74 mmol) were dissolved in DCM (1 mL) at 0° C.

DIPEA (150 µL, 0.81 mmol) was added. This was stirred at 0° C for 15 minutes. The reaction mixture was loaded directly on a silica column. Purification by silica chromatography (0-50% EtOAc in DCM) yielded tert-butyl (R)-3-((6-chloro-1,2,4,5-tetrazin-3-yl)amino)piperidine-1-carboxylate (200 mg, 97%) as a red solid. ^{1}H NMR (acetone-d6) δ: 7.80 (br s, 1H), 3.95-4.10 (m, 2H), 3.65-3.79 (m, 1H), 3.05-3.40 (m, 2H), 2.12-2.19 (m, 1H), 1.73-1.90 (m, 2H), 1.50-1.63 (m, 1H), 1.41 (s, 9H).

Step 2. tert-Butyl (R)-3-((4-chloro-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate

Tert-butyl (R)-3-((6-chloro-1,2,4,5-tetrazin-3-yl)amino)piperidine-1-carboxylate (100 mg, 0.32 mmol), (cyclohept-1-en-1-yloxy)trimethylsilane (68 mg, 0.37 mmol) and toluene (0.3 mL) were heated at 120° C in a sealed tube under argon for 15 hours. The reaction mixture was loaded directly on a silica column. Purification by silica chromatography (0-50% EtOAc in DCM) yielded (R)-4-chloro-N-(1-methylpiperidin-3-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-amine (47 mg, 39%) as a reddish semisolid. MS *m/z* 380.6 $[M+H]^+$; ^{1}H NMR (acetone-d6) δ: 5.55 (br s, 1H), 4.10-4.20 (br s, 1H), 4.04 (d, J = 14 Hz, 1H), 3.66-3.75 (m, 1H), 3.00-3.20 (m, 2H), 2.97 (t, J = 5.6, 2H), 2.76 (t, J = 5.6, 2H), 1.91 (t, J = 5.6, 2H), 1.50-1.80 (m, 8H), 1.43 (s, 9H).

Intermediate 23: tert-Butyl (R)-3-((4-chloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate



Step 1: ((5,5-Dimethylcyclopent-1-en-1-yl)oxy)trimethylsilane

LDA (2M in THF, 4.8 L, 9.6 mmol) was cooled to -78°C. A solution of 2,2-dimethylcyclopentan-1-one (1g, 8.9 mmol) was added dropwise. This was stirred at -78°C for 30 minutes. Chlorotrimethylsilane (2 mL, 15.7 mmol) was then added dropwise. The mixture was warmed to room temperature over 90 minutes, then quenched with saturated aqueous $NaHCO_3$, and diluted with pentane. The bilayer was filtered through celite. The organic layer was

separated, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica gel chromatography (hexanes) yielded ((5,5-dimethylcyclopent-1-en-1-yl)oxy)trimethylsilane at 90 % purity. (923 mg, 50%). ^{1}H NMR (acetone-d6) δ: 4.49 (s, 1H), 2.15 (t, J = 7.5 Hz, 2H), 1.69 (t, J = 7.5 Hz, 2H), 1.00 (s, 6H), 0.21 (s, 9H).

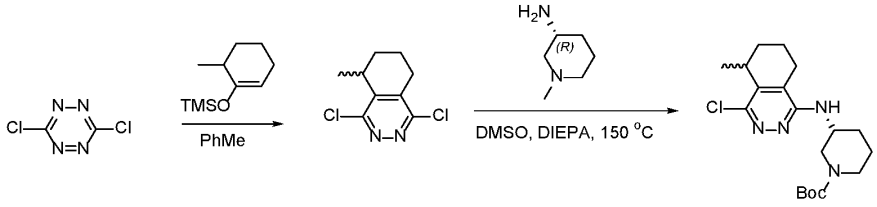
Step 2. 1,4-Dichloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazine

((5,5-Dimethylcyclopent-1-en-1-yl)oxy)trimethylsilane (750 mg, 4.07 mmol), toluene (4 mL), and 3,6-dichloro-1,2,4,5-tetrazine (610 mg, 4.04 mmol) were heated under argon at 120° C for 15 hours. Toluene was then removed by nitrogen stream. Purification by silica gel chromatography (0-10% EtOAc in DCM), followed by hexane trituration, yielded 1,4-dichloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (360 mg, 41%) as a light pink solid. ^{1}H NMR (acetone-d6) δ: 3.09 (t, J = 7.5 Hz, 2H), 2.14 (t, J = 7.5 Hz, 2H), 1.47 (s, 6H).

Step 3: tert-Butyl (R)-3-((4-chloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate

1,4-Dichloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazine (500 mg, 2.3 mmol), (R)-1-Boc-3-aminopiperidine (520 mg, 2.5 mmol), DIPEA (1.35 mL, 7.74 mmol) and NMP (5.4 mL) were heated at 120° C for 4 days, then partitioned between H_2O and EtOAc. The organic layer was back-washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica gel chromatography (0-100% EtOAc in DCM), followed by hexane trituration, yielded tert-butyl (R)-3-((4-chloro-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate (166 mg, 19%) as a white solid, which was applied to the next step without further purification.

Intermediate 25: tert-Butyl (3R)-3-((4-chloro-5-methyl-5,6,7,8-tetrahydrophthalazin-1-yl)amino)piperidine-1-carboxylate



Step 1: 1,4-Dichloro-5-methyl-5,6,7,8-tetrahydrophthalazine

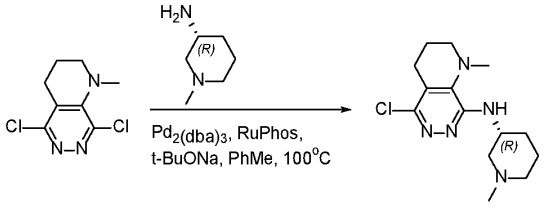
3,6-Dichloro-1,2,4,5-tetrazine (200 mg, 1.32 mmol, 1.0 eq.) and trimethyl((6-methylcyclohex-1-en-1-yl)oxy)silane (317 mg, 1.3 eq) were mixed in anhydrous toluene (1.0

mL) under argon. The mixture was heated to 120°C for 2 hr in a sealed tube. After cooling and concentrated, the crude material was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexane to provide 1,4-dichloro-5-methyl-5,6,7,8-tetrahydrophthalazine (89 mg, 30 % yield). ^{1}H NMR (acetone-d6) δ: 2.97 (dt, *J*=6.91, 3.4 Hz, 1 H), 2.65 - 2.74 (m, 1 H), 2.35 - 2.54 (m, 1 H), 1.72 - 1.81 (m, 2 H), 1.62 - 1.69 (m, 2 H), 1.09 - 1.13 (d, *J*=6.91, 3 H).

Step 2. tert-Butyl (3R)-3-((4-chloro-5-methyl-5,6,7,8-tetrahydrophthalazin-1-yl)amino) piperidine-1-carboxylate

1,4-Dichloro-5-methyl-5,6,7,8-tetrahydrophthalazine (56 mg, 0.26 mmol), (R)-1-Boc-3-aminopiperidine (56 mg, 0.26 mmol), DIPEA (68 mg, 0.52 mmol) and NMP (0.5 mL) were heated at 130° C for 2 days, then partitioned between H_2O and EtOAc. The organic layer was back-washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica gel chromatography (0-100% EtOAc in DCM), followed by hexane trituration, yielded tert-butyl (3R)-3-((4-chloro-5-methyl-5,6,7,8-tetrahydrophthalazin-1-yl)amino) piperidine-1-carboxylate (25 mg, 25%), which was applied to the next step without further purification. MS *m/z* 381.1 $[M+H]^+$.

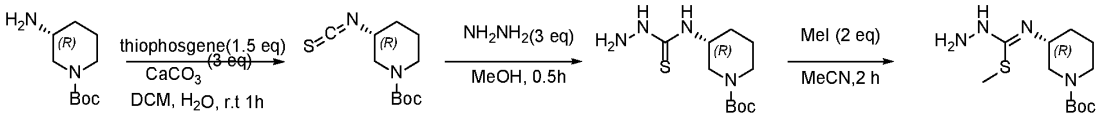
Intermediate 26: (R)-5-Chloro-1-methyl-N-(1-methylpiperidin-3-yl)-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-8-amine



A solution of 5,8-dichloro-1-methyl-3,4-dihydro-2H-pyrido[2,3-d]pyridazine (prepared according to WO2020239076A1, 200 mg, 0.92 mmol), (3R)-1-methylpiperidin-3-amine (127 mg, 1.1 mmol), RuPhos (47 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium (88 mg, 0.1 mmol) and sodium tert-butoxide (187 mg, 2 mmol) in toluene (5 mL) was stirred at 100°C for 12 hours under N_2 atmosphere. After the reaction, solvent was removed and the crude residue was purified over silica gel using 30% EA/PE to give (R)-5-chloro-1-methyl-N-(1-methylpiperidin-3-yl)-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-8-amine (70 mg, 26% Yield). MS *m/z* 296.2

$[M+H]^+$.

Intermediate 27: tert-Butyl (R,Z)-3-((hydrazineyl(methylthio)methylene)amino)piperidine-1-carboxylate



Step 1. tert-Butyl (R)-3-isothiocyanatopiperidine-1-carboxylate

To a solution of $CaCO_3$ (7.5 g, 75 mmol) in DCM (100 mL) and water (50 mL) was added slowly tert-butyl (3R)-3-aminopiperidine-1-carboxylate (5.0 g, 25 mmol) and thiophosgene (4.3 g, 37 mmol) at 0 °C under N2. Then the reaction mixture was stirred at room temperature for 1h. The mixture was filtered and the filtrate was extracted with DCM (2 x 50 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuum. The crude product was purified on silica gel eluted with PE/EA=8:1 to give the compound tert-butyl (R)-3-isothiocyanatopiperidine-1-carboxylate (6.0 g, 99.2% Yield) as a pale yellow oil. MS *m/z* 143 $[M\text{-Boc}+H]^+$.

Step 2. tert-Butyl (R)-3-(hydrazinecarbothioamido)piperidine-1-carboxylate

To a solution of tert-butyl (R)-3-isothiocyanatopiperidine-1-carboxylate (6.0 g, 25 mmol) in methanol (50 mL) was added hydrazine in water (3.6 mL, 93 mmol, 80%) under N_2, then the reaction mixture was stirred at 25°C for one hour, evaporated in vacuum, then brine(80 mL) was added and extracted with DCM(2 x 80 mL), dried over Na_2SO_4, evaporated in vacuum to give compound tert-butyl (R)-3-(hydrazinecarbothioamido)piperidine-1-carboxylate (6.0 g, 99.2% Yield) as a pale yellow oil, which could be used next step without further purification. MS *m/z* 275.1 $[M+H]^+$.

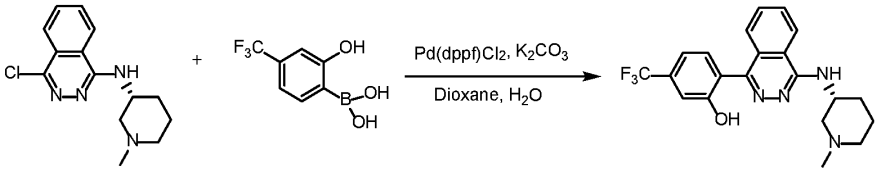
Step 3. tert-Butyl (R)-3-isothiocyanatopiperidine-1-carboxylate

To a solution of tert-butyl (3R)-3-(aminocarbamothioylamino)piperidine-1-carboxylate (6.0 g, 21.9 mmol) in ACN (60 mL) was added MeI (6.2 g, 43.8 mmol) at 0°C under N_2. The reaction mixture was stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure, diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ (2 x 40 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude product was purified on silica

gel eluted with (PE/EA=2:1) to give the compound tert-butyl (R)-3-isothiocyanatopiperidine-1-carboxylate (1.9 g, 30.2% Yield) as a brown oil. MS *m/z* 289.0 $[M+H]^+$. ^1H NMR (CHLOROFORM-d) δ: 10.21 (br s, 1H), 3.70-3.78 (m, 2H), 3.47 (br s, 1H), 3.38 (br s, 2H), 2.97 (s, 3H), 1.95-2.04 (m, 1H), 1.73-1.85 (m, 2H), 1.56-1.66 (m, 1H), 1.47 (s, 9H)

Example 1

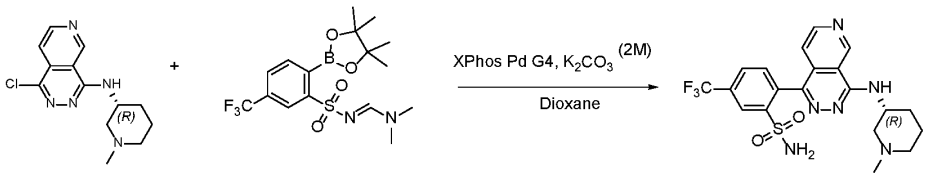
Preparation of Compound I-1



To a solution of 4-chloro-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (Intermediate 19a, 55 mg, 0.20 mmol) in 1,4-dioxane (4 mL) was added [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (1.2 eq., 0.24 mmol), and potassium carbonate in water (2 M water solution), and bubbled nitrogen through for 5 minutes. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.1 eq., 0.020 mmol) was then added and the reaction mixture was kept bubbling nitrogen for another 5 min before . and then the reaction vessel was sealed. The reaction was heated to 100°C for 3 h. The reaction mixture was purified by C18 reverse phase EZ-Prep using formic acid as the additive to give 2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (35 mg, 44% yield) as formic acid salt. MS *m/z* 403.0 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 8.52 (s, 1H, formic acid proton), 8.32 (br d, J=8.1 Hz, 1H), 7.87-7.95 (m, 1H), 7.79-7.87 (m, 1H), 7.62 (br d, J=8.1 Hz, 1H), 7.52 (br d, J=7.9 Hz, 1H), 7.28-7.36 (m, 1H), 7.28 (s, 1H), 4.60-4.70 (m, 1H), 3.54-3.69 (m, 1H), 3.13-3.24 (m, 1H), 2.76-2.92 (m, 2H), 2.76 (s, 3H), 2.03-2.25 (m, 2H), 1.77-1.98 (m, 2H). NH and OH not observed.

Example 2

Preparation of Compound I-156



A solution of 1-chloro-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (Intermediate 20a, 145 mg, 0.5 mmol), (E)-N,N-dimethyl-N'-((2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl)sulfonyl)formimidamide (Intermediate 10, 300 mg, 0.75 mmol), XPhos Pd G4 (43 mg, 0.05 mmol) and potassium carbonate (138 mg, 1 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was stirred at 100 °C under N_2 for 2 h. After that, some starting material remains, so another portion of XPhos Pd G4 (43 mg, 0.05 mmol) was added in and the solution was stirred for another 2 h at 100 °C under N_2, monitored by LCMS. After that, the mixture was washed with water and brine, dried over Na_2SO_4, concentrated and purified by Prep-HPLC to give (R)-2-(4-((1-methylpiperidin-3-yl)amino)pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzene-sulfonamide (35 mg, 20 % yield) as yellow solid. MS *m/z* 467.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.49 (s, 1H), 8.93 (d, J = 5.4 Hz, 1H), 8.32 (s, 1H, formic acid), 8.30 – 8.23 (m, 2H), 7.90 – 7.85 (m, 1H), 7.76 – 7.70 (m, 1H), 4.20 – 4.10 (m, 1H), 3.25 – 3.15 (m, 1H), 2.92 – 2.79 (m, 1H), 2.45 (s, 3H), 2.41 – 2.26 (m, 2H), 2.08 – 1.99 (m, 1H), 1.98 – 1.88 (m, 1H), 1.82 – 1.69 (m, 1H), 1.65 – 1.53 (m, 1H).

The compounds below were prepared according to the procedure of Examples 1 or 2 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-2	MS *m/z* 407.2 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.36 (s, 2H, formic acid), 7.37 (d, J=7.8 Hz, 1H), 7.26 (d, J=8.0 Hz, 1H), 7.20 (s, 1H), 4.51-4.65 (m, 1H), 3.63-3.85 (m, 1H), 3.35-3.42 (m, 1H), 2.95-3.12 (m, 2H), 2.87 (s, 3H), 2.50 (dt, J=17.7, 6.2 Hz, 4H), 2.04-2.23 (m, 2H), 1.86-1.98 (m, 3H), 1.72-1.86 (m, 3H)
I-3	MS *m/z* 393.3 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.41 (br s, 2H, formic acid proton), 7.72 (br d, J=7.8 Hz, 1H), 7.16-7.28 (m, 2H), 4.53 (br s, 1H), 3.64-3.82 (m, 1H), 3.35-3.46 (m, 1H), 3.10-3.25 (m, 2H), 2.92-3.07 (m, 3H), 2.78-2.89 (m, 4H), 2.12-2.28 (m, 4H), 1.95 (br d, J=10.4 Hz, 1H), 1.81 (br s, 1H).
I-4	MS *m/z* 409.0 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.35 (s, 1H), 8.05 (br d, J=5.4 Hz, 1H), 7.97 (br d, J=8.0 Hz, 1H), 7.81 (br d, J=5.4 Hz, 1H), 7.15-7.26 (m, 2H), 4.46-4.63 (m, 1H), 3.57-3.73 (m, 1H), 2.83-2.97 (m, 1H), 2.74 (s, 3H), 2.57 (s,

Compound	Spectral Data
	1H), 1.97-2.19 (m, 2H), 1.80-1.94 (m, 1H), 1.67-1.80 (m, 1H), NH and OH not observed
I-5	MS *m/z* 404.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.09 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.01 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.81 (dd, *J* = 8.3, 4.4 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 1H), 4.55 – 4.47 (m, 1H), 3.06 (s, 1H), 2.73 – 2.55 (m, 1H), 2.48 – 2.25 (m, 5H), 2.12 – 1.96 (m, 1H), 1.94 – 1.83 (m, 1H), 1.81 – 1.63 (m, 2H), NH and OH not observed.
I-6	MS *m/z* 375.1 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.55 (d, J=8.3 Hz, 1H), 8.06-8.15 (m, 1H), 7.96-8.06 (m, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.29-7.43 (m, 2H), 3.59-3.83 (m, 3H), 3.43-3.58 (m, 1H), 3.35-3.39 (m, 1H), 2.53-2.64 (m, 1H), 2.41-2.53 (m, 1H), NHs and OH not observed.
I-7	MS *m/z* 404.3 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 9.62 (s, 1H), 8.76 (d, J=5.5 Hz, 1H), 7.44-7.55 (m, 1H), 7.39 (br d, J=5.6 Hz, 1H), 7.10-7.32 (m, 2H), 4.55 (br s, 1H), 2.97-3.17 (m, 1H), 2.64 (br s, 1H), 2.52-2.29 (m, 5H), 2.00 (br s, 1H), 1.75-1.87 (m, 1H), 1.55-1.75 (m, 2H), NH and OH not observed.
I-8	MS *m/z* 417.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.20 (br d, J=8.1 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 7.70 (br d, J=7.0 Hz, 1H), 7.41-7.50 (m, 1H), 7.31 (br d, J=7.6 Hz, 1H), 7.20 (s, 1H), 4.57-4.77 (m, 1H), 3.80-3.97 (m, 1H), 3.68 (s, 1H), 3.39-3.56 (m, 1H), 2.97-3.11 (m, 2H), 2.86-2.97 (m, 3H), 2.23 (br s, 1H), 2.18 (s, 3H), 1.88-2.08 (m, 2H), NH and OH not observed.
I-9	MS *m/z* 421.0 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.41-8.47 (m, 1H), 7.70-7.77 (m, 1H), 7.55 (br d, J=7.6 Hz, 1H), 7.34 (br d, J=7.1 Hz, 1H), 7.29 (br s, 1H), 7.24 (br d, J=8.9 Hz, 1H), 4.82 (br s, 1H), 4.70 (br s, 1H), 3.77-3.97 (m, 1H), 3.45 (br s, 1H), 3.13 (br s, 1H), 2.93 (br s, 3H), 2.11-2.33 (m, 2H), 1.84-2.10 (m, 2H)
I-12	MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.36 (s, 2H, formic acid), 7.90-7.95 (m, 1H), 7.85 (br t, J=7.4 Hz, 1H), 7.64 (br d, J=8.0 Hz, 1H), 7.54 (br d, J=7.8 Hz, 1H), 7.22-7.42 (m, 2H), 4.65-4.83 (m, 1H), 3.83 (br s, 1H), 3.35-3.46 (m, 1H), 3.03-3.25 (m, 2H), 2.89 (br s, 3H), 2.33-2.13 (m, 2H), 1.88-2.10 (m, 2H), 1H buried under FA peak, NH and OH not observed.
I-23	MS *m/z* 407.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.45 (s, 1H, formic acid), 7.29 (br d, J=7.6 Hz, 1H), 7.15 (br d, J=7.9 Hz, 1H), 7.07 (s, 1H), 4.33 (br s, 1H), 3.53 (br d, J=10.5 Hz, 1H), 3.13-3.19 (m, 1H), 2.73-2.90 (m, 3H), 2.23-2.52 (m, 2H), 2.00-2.14 (m, 1H), 1.88-2.00 (m, 1H), 1.79-1.88 (m, 2H), 1.65-1.79 (m, 3H), 1.57-1.65 (m, 1H), 0.79 (br d, J=7.0 Hz, 3H). OH and NH not observed.
I-33	MS *m/z* 335.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.64 (s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.80 – 7.73 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.06 – 6.92 (m, 3H), 4.48 – 4.35 (m, 1H), 3.15 – 3.03 (m, 1H), 2.77 – 2.64 (m, 1H), 2.22 (s, 3H), 2.04 – 1.87 (m, 3H), 1.81 – 1.71 (m, 1H), 1.67 – 1.55 (m, 1H), 1.52 – 1.42 (m, 1H).
I-54	MS *m/z* 404.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.95 (s, 1H), 8.92 (d, J=5.8 Hz, 1H), 8.24 (d, J=5.8 Hz, 1H), 7.63 (d, J=7.9 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.29 (s, 1H), 4.55-4.67 (m, 1H), 3.16-3.29 (m, 1H), 2.79 (br s, 1H), 2.42 (s, 4H), 2.10 (br s, 1H), 1.86-1.98 (m, 1H), 1.79 (br dd, J=10.1, 3.6 Hz, 1H), 1.70 (br s, 1H), 1.11-1.21 (m, 1H), NH and OH not observed.

Compound	Spectral Data
I-64	MS *m/z* 431.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.35-8.42 (m, 1H), 8.20 (s, 1H), 7.92-8.04 (m, 1H), 7.83-7.91 (m, 1H), 7.61-7.75 (m, 1H), 7.56 (br d, J=7.0 Hz, 1H), 7.31-7.38 (m, 1H), 4.30-4.41 (m, 2H), 3.20 (br dd, J=12.5, 9.4 Hz, 1H), 3.10 (br d, J=10.4 Hz, 1H), 2.90 (br d, J=14.6 Hz, 1H), 2.27 (br dd, J=12.4, 3.9 Hz, 1H), 2.19 (s, 3H), 1.83-1.97 (m, 2H), 1.66 (br d, J=12.5 Hz, 1H). NH and OH not observed.
I-66	MS *m/z* 404.2 $[M+H]^+$.^1H NMR (400 MHz, CD_3OD) δ 9.15 (d, *J* = 4.5 Hz, 1H), 8.82 (d, *J* = 8.3 Hz, 1H), 8.54 (s, 1H, formic acid), 8.43 (d, *J* = 8.1 Hz, 1H), 7.96 – 7.86 (m, 1H), 7.28 – 7.20 (m, 2H), 4.60 (s, 1H), 2.94 – 2.77 (m, 1H), 2.61 – 2.38 (m, 5H), 2.18 – 2.03 (m, 1H), 2.02 – 1.89 (m, 1H), 1.90 – 1.59 (m, 2H).
I-67	MS *m/z* 370.1 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 8.90 (d, J = 4.5 Hz, 1H), 8.26 (s, 1H, formic acid), 7.84 (d, J = 8.3 Hz, 1H), 7.63 (dd, J = 8.4, 4.4 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.82 (s, 1H), 4.43 – 4.33 (m, 1H), 3.58 – 3.31 (m, 1H), 3.07-2.97 (m, 1H), 2.90 – 2.64 (m, 2H), 2.58 (s, 3H), 2.05 – 1.85 (m, 2H), 1.79 – 1.53 (m, 2H), NH and OH not observed
I-73	MS *m/z* 366.1 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 9.66 (s, 1H), 8.80 (d, J=5.5 Hz, 1H), 7.46 (dd, J=5.8, 0.8 Hz, 1H), 7.12 (dd, J=6.8, 2.8 Hz, 1H), 6.94-7.00 (m, 2H), 4.57-4.65 (m, 1H), 3.94 (s, 3H), 3.03-3.24 (m, 1H), 2.63-2.79 (m, 1H), 2.29-2.41 (m, 5H), 2.01-2.13 (m, 1H), 1.83-1.93 (m, 1H), 1.59-1.82 (m, 2H). NH and OH not observed
I-85	MS *m/z* 392.9 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 8.48 (d, J=8.3 Hz, 1H), 8.40 (s, 1H, formic acid), 7.57 (br d, J=7.6 Hz, 1H), 7.45 (s, 1H), 7.34 (br d, J=8.5 Hz, 1H), 7.28 (s, 1H), 4.26-4.37 (m, 1H), 3.01 (br d, J=8.8 Hz, 1H), 2.67 (br d, J=10.5 Hz, 1H), 2.21 (s, 3H), 1.86-2.03 (m, 3H), 1.70-1.81 (m, 1H), 1.60 (br d, J=12.5 Hz, 1H), 1.30-1.45 (m, 1H), NH and OH not observed.
I-95	MS *m/z* 417.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.26 (d, J = 8.2 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.86 – 7.80 (m, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 1.7 Hz, 1H), 4.59 (s, 1H), 3.29 – 3.20 (m, 1H), 3.16 – 2.98 (m, 2H), 2.95 – 2.82 (m, 1H), 2.64 (s, 3H), 2.27 – 2.14 (m, 1H), 2.09 – 1.61 (m, 5H). NH and OH not observed
I-108	MS *m/z* 419.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 10.36 (br s, 1H), 8.30 (d, J=8.3 Hz, 1H), 7.87 (t, J=7.2 Hz, 1H), 7.79 (t, J=7.5 Hz, 1H), 7.52 (br d, J=7.8 Hz, 2H), 7.45 (d, J=8.0 Hz, 1H), 7.30 (d, J=7.8 Hz, 1H), 7.28 (s, 1H), 3.74 (q, J=6.4 Hz, 2H), 3.57-3.65 (m, 4H), 2.57-2.79 (m, 2H), 2H under DMSO peak.
I-109	MS *m/z* 361.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 7.95-8.11 (m, 1H), 7.65 (dt, J=5.0, 2.4 Hz, 2H), 7.46 (br d, J=7.8 Hz, 1H), 7.19-7.29 (m, 2H), 7.08-7.19 (m, 1H), 4.19 (br d, J=6.8 Hz, 2H), 3.99 (s, 1H), 3.22-3.45 (m, 4H), 2.71-2.83 (m, 1H).
I-113	MS *m/z* 418.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.66 (s, 1H), 8.94 (d, J = 5.6 Hz, 1H), 8.55 (s, 1H, formic acid), 7.56 (dd, J = 15.4, 6.7 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 4.17 – 4.03 (m, 1H), 4.03 – 3.92 (m, 1H), 3.87 – 3.70 (m, 1H), 3.69 – 3.49 (m, 2H), 3.21 – 3.01 (m, 2H), 2.38 – 2.21 (m, 1H), 2.18 – 1.88 (m, 3H), 1.43 (t, J = 7.3 Hz, 3H). NH and OH not observed

Compound	Spectral Data
I-117	MS *m/z* 423.8 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ: 7.83 (br d, J=7.6 Hz, 1H), 7.10-7.34 (m, 2H), 4.37 (br s, 4H), 3.42-3.55 (m, 1H), 3.09-3.31 (m, 1H), 2.78-2.93 (m, 1H), 2.74 (s, 3H), 2.41-2.64 (br s, 3H), 1.96-2.15 (m, 3H), 1.77-1.94 (m, 2H), 1.65-1.77 (m, 1H). NH and OH not observed
I-119	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 9.72 (s, 1H), 8.87 (d, J=5.8 Hz, 1H), 8.26 (s, 3H, formic acid), 7.61 (br d, J=7.8 Hz, 1H), 7.43-7.53 (m, 2H), 7.38 (d, J=5.8 Hz, 1H), 4.66-4.80 (m, 1H), 3.93-3.83 (m, 1H), 3.80 (s, 3H), 3.38-3.55 (m, 1H), 3.05-3.17 (m, 2H), 2.92 (s, 3H), 2.15-2.37 (m, 2H), 1.86-2.07 (m, 2H), NH and OH not observed.
I-120	MS *m/z* 452.9 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ: 8.45 - 8.37 (m, 2 H, including formic acid), 7.96 (t, J = 7.69 Hz, 1 H), 7.87 (t, J = 7.63 Hz, 1 H), 7.82 - 7.72 (m, 2 H), 7.70 (s, 1 H), 7.52 (d, J = 8.13 Hz, 1 H), 6.90 (td, J = 73.92 Hz, 11.51 Hz, 1 H), 4.77 - 4.60 (m, 1 H), 3.96 - 3.75 (m, 1 H), 3.54 - 3.37 (m, 1 H), 3.16 – 2.98 (m, 2 H), 2.91 (s, 3 H), 2.36 - 2.12 (m, 2 H), 2.06 - 1.82 (m, 2 H). 1H not observed (NH).
I-121-	MS *m/z* 454.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ: 9.83 (s, 1 H), 8.86 (d, J = 5.63 Hz, 1 H), 7.85 – 7.76 (m, 3 H), 7.75 (s, 1 H), 7.35 (t, J = 73.17 Hz, 1 H), 7.27 (d, J = 5.63 Hz, 1 H), 4.53 – 4.44 (m, 1 H), 3.15 – 3.06 (m, 1 H), 2.77 – 2.68 (m, 1 H), 2.23 (s, 3 H), 2.05 - 1.85(m, 3 H), 1.83 - 1.73 (m, 1 H), 1.70 - 1.54 (m, 1 H), 1.52 - 1.41 (m, 1 H)
I-127	MS *m/z* 405.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.48 (d, J = 8.0 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.88 – 7.77 (m, 3H), 7.52 – 7.46 (m, 1H), 7.35 (d, J = 7.2 Hz, 1H), 4.54 – 4.41 (m, 1H), 3.19 – 3.06 (m, 1H), 2.84 – 2.70 (m, 1H), 2.28 (s, 3H), 2.09 – 1.91 (m, 3H), 1.84 – 1.74 (m, 1H), 1.71 – 1.59 (m, 1H), 1.52 – 1.42 (m, 1H).
I-128	MS *m/z* 406.2 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 9.77 (s, 1H), 8.95 (d, J = 5.5 Hz, 1H), 8.47 (s, 1H, formic acid), 7.50-7.90 (m, 3H), 7.51 (br s, 1H), 4.72-4.79 (m, 1H), 3.60-3.75 (m, 1H), 3.29-3.32 (m, 1H), 2.80-3.00 (m, 2H), 2.67 (s, 3H), 2.10-2.30 (m, 2H), 1.83-2.00 (m, 2H). -NH not observed
I-129	MS *m/z* 372.1, 374.1 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 9.76 (s, 1H), 8.94 (d, J = 5.5 Hz, 1H), 8.47 (s, 1H, formic acid), 7.62 (t, J = 8 Hz, 1H), 7.45-7.55 (m, 3H), 4.70-4.78 (m, 1H), 3.65-3.75 (m, 1H), 2.85-3.00 (m, 2H), 2.82 (s, 3H), 2.10-2.28 (m, 2H), 1.78-2.02 (m, 2H). One proton is hidden under the residual deutero methanol peak at 3.33 ppm.
I-131	MS *m/z* 412.0 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.31-8.47 (m, 1H), 8.19 (br d, J=7.6 Hz, 1H), 7.81-8.01 (m, 4H), 7.60 (br d, J=8.1 Hz, 1H), 4.65 (dt, J=8.3, 4.0 Hz, 1H), 2.74-2.97 (m, 2H), 2.50 (s, 5H), 2.08-2.16 (m, 1H), 1.91-2.01 (m, 1H), 1.71-1.89 (m, 2H).
I-138	MS *m/z* 438.1 $[M+H]^+$; ^1H NMR (CHLOROFORM-d) δ: 9.50 (br s, 1H), 8.89 (d, J=5.8 Hz, 1H), 8.15 (s, 1H), 7.87 (d, J=8.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.29 (d, J=5.5 Hz, 1H), 7.01 (t, J=55.5 Hz, 1H), 6.69 (br dd, J=7.2, 4.1 Hz, 1H), 4.81 (br s, 1H), 2.84 (br s, 2H), 2.44-2.61 (m, 1H), 2.36 (s, 3H), 2.06-2.28 (m, 2H), 1.80-1.98 (m, 1H), 1.67-1.73 (m, 2H)

Compound	Spectral Data
I-139	MS *m/z* 370.0 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 9.98 (br s, 1H), 9.81 (s, 1H), 8.84 (d, J=5.5 Hz, 1H), 7.66 (br d, J=7.3 Hz, 1H), 7.36 (t, J=8.2 Hz, 1H), 7.04-7.12 (m, 2H), 6.97-7.02 (m, 1H), 4.42-4.53 (m, 1H), 3.09-3.17 (m, 1H), 2.71-2.80 (m, 1H), 2.19-2.31 (m, 3H), 1.89-2.10 (m, 3H), 1.79 (br d, J=11.0 Hz, 1H), 1.63 (br d, J=12.5 Hz, 1H), 1.49 (br dd, J=10.7, 4.9 Hz, 1H)
I-140	MS *m/z* 361.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.4 (bs, 1H), 9.82 (s, 1H), 8.85 (d, J= 4.0 Hz, 1H),7.78-7.75 (m, 1H), 7.56-7.52 (m, 1H), 7.46 (d, J= 4.0 Hz, 1H), 7.32 (d, J= 8.0 Hz, 1H), 7.17 (d, J= 8.0 Hz, 1H), 4.49 (bs, 1H), 3.35-3.30 (m, 1H), 3.12-3.08 (m, 1H), 2.23 (d, J= 8.0 Hz, 3H), 2.03-1.94 (m, 3H), 1.78-1.76 (m, 1H), 1.64-1.61 (m, 1H), 1.50-1.44 (m, 1H).
I-154	MS *m/z* 422.0 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ: 7.61 (br d, J=8.0 Hz, 1H), 7.23-7.29 (m, 1H), 7.18-7.22 (m, 1H), 4.38 (br s, 1H), 3.52-3.74 (m, 1H), 3.35-3.51 (m, 2H), 3.01 (br s, 1H), 2.77-2.96 (m, 4H), 2.50-2.62 (m, 5H), 2.12 (br s, 2H), 1.88-2.09 (m, 4H), 1.79 (br s, 1H).
I-155	MS *m/z* 388.4, 390.3 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 7.55 (br d, J=8.5 Hz, 1H), 6.90-6.99 (m, 2H), 4.36 (br dd, J=3.1, 2.1 Hz, 1H), 3.50 (br s, 1H), 3.12-3.25 (m, 4H), 2.96-3.08 (m, 1H), 2.62-2.73 (m, 1H), 2.46-2.58 (m, 4H), 2.38 (s, 3H), 1.93-2.08 (m, 3H), 1.80-1.89 (m, 1H), 1.67-1.80 (m, 1H), 1.54-1.66 (m, 1H), OH and NH not observed.
I-159	MS *m/z* 350.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 11.8 (bs, 1H), 8.34 (d, J=8 Hz, 1H), 7.83-7.80 (m, 2H), 7.76-7.72 (m, 2H),7.50 (d, J=8 Hz, 1H), 7.05 (bs, 1H), 4.4 (bs, 1H), 3.34-3.30 (m, 2H), 2.84-2.82 (m, 2H), 2.35-2.32 (bs, 3H), 2.01-1.99 (m, 1H), 1.95 (s, 3H), 1.80-1.78 (m, 1H), 1.65-1.62 (m, 1H), 1.50-1.45 (m, 1H).
I-160	MS *m/z* 364.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 8.39 (d, J=8.0 Hz, 1H), 7.84 (t, J=7.1 Hz, 1H), 7.73-7.80 (m, 1H), 7.66 (d, J=7.3 Hz, 1H), 7.35 (d, J=7.8 Hz, 1H), 7.11 (br d, J=7.5 Hz, 1H), 7.03 (d, J=7.3 Hz, 1H), 4.36-4.46 (m, 1H), 3.74 (s, 3H), 3.05-3.13 (m, 1H), 2.68-2.76 (m, 1H), 2.51 (s, 3H), 2.22 (s, 3H), 1.84-2.05 (m, 3H), 1.70-1.81 (m, 1H), 1.61 (br d, J=11.8 Hz, 1H), 1.46 (br dd, J=11.5, 3.3 Hz, 1H)
I-165	MS *m/z* 366.1 $[M+H]^+$ 369.7; ^1H NMR (400 MHz, METHANOL-d4) δ: 8.43 (br s, 1H, formic acid peak), 8.25 (d, J=8.3 Hz, 1H), 7.84 (s, 1H), 7.77 (s, 1H), 7.45-7.62 (m, 1H), 7.13 (br d, J=1.5 Hz, 2H), 4.40-4.69 (m, 1H), 3.26-3.56 (m, 1H), 2.89-3.07 (m, 1H), 2.53 (br s, 5H), 2.34 (s, 3H), 1.97-2.13 (m, 1H), 1.86-1.97 (m, 1H), 1.62-1.86 (m, 2H). OH and NH not observed.
I-166	MS *m/z* 388.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.73 (s, 1H), 8.90 (d, J=5.8 Hz, 1H), 7.84-7.92 (m, 4H), 7.72 (d, J=5.6 Hz, 1H), 4.58-4.71 (m, 1H), 3.06-3.25 (m, 1H), 2.73 (br s, 1H), 2.30-2.45 (m, 4H), 2.08 (br s, 1H), 1.85-1.95 (m, 1H), 1.66-1.85 (m, 2H)
I-167	MS *m/z* 411.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ9.74 (s, 1H), 8.93 (d, J= 5.6 Hz, 1H),7.86-7.83 (m, 2H), 7.77-7.75(m, 1H), 7.44-7.42 (m, 1H), 6.92(t, J= 72.8 Hz, 1H), 4.75-4.68 (m, 1H),4.03-4.01 (m, 1H), 3.61-3.57(m, 1H), 3.06-3.00 (m, 1H), 2.97 (s, 3H), 2.94-2.87 (m, 1H), 2.37-2.32 (m, 1H), 2.21-2.18(m, 1H), 2.08-1.84 (m, 2H). NH not observed

Compound	Spectral Data
I-168	MS *m/z* 400.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.87(s, 1H), 9.05(d, J= 5.64Hz, 1H), 7.63(dd, J= 7.56, 1.93 Hz, 1H), 7.55(d, J= 5.63Hz, 1H), 7.53 – 7.40 (m, 2H), 6.46 (t, J= 73.6 Hz, 1H), 4.70 (d, J= 12.9 Hz, 1H), 3.98 (d, J= 11.8 Hz, 1H), 3.60 (d, J= 12.5 Hz, 1H), 3.03 (d, J = 11.3 Hz, 2H), 2.98 (s, 3H), 2.45 (s, 3H), 2.35 (s, 1H), 2.21–2.12 (m, 1H), 2.10 – 1.8 (m, 2H). -NH not observed
I-169	MS *m/z* 481.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.33 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.31-7.30 (m, 1H), 7.12 (d, J = 5.6Hz, 1H), 4.51-4.50 (m, 1H), 3.29 (s, 1H), 3.18 (s, 1H), 2.82 (s, 1H), 2.43 (d, J = 4.8 Hz, 3H), 2.33-2.31 (m, 3H), 2.06-2.03 (m, 2H), 1.82-1.80 (m, 1H), 1.66-1.62 (m, 1H), 1.53-1.50 (m, 1H).
I-171	MS *m/z* 415.4 $[M-H_2O+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.83 (s, 1H), 8.93 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 5.6 Hz, 1H), 7.29 (t, J = 36 Hz, 1H), 7.03 (t, J = 2.0, 8.4 Hz 1H), 4.71-4.65 (m, 1H), 3.89(s, 3H), 3.55-3.48 (m, 1H), 2.99-2.83 (m, 5H), 2.18 (d, J = 10.4 Hz, 1H), 2.06-2.00 (m, 1H), 1.92-1.69 (m, 2H)
I-175	MS *m/z* $[M+H]^+$: 366.4; ^1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1 H), 8.84 (d, J = 5.63 Hz, 1 H), 7.51 (d, J = 7.50 Hz, 1 H), 7.34 (d, J = 5.63 Hz, 1 H), 7.25 (d, J = 8.25 Hz, 1 H), 6.63 - 6.50 (m, 2 H), 4.48 - 4.37 (m, 1 H), 3.79 (s, 3 H), 3.10 (d, J = 8.25 Hz, 1 H), 2.72 (d, J = 10.8 Hz, 1 H), 2.22 (s, 3 H), 2.06 - 1.85 (m, 3 H), 1.83 - 1.70 (m, 1 H), 1.69 - 1.54 (m, 1 H), 1.53 - 1.37 (m, 1 H). 1H not observed (OH)
I-177	MS *m/z* $[M+H]^+$: 456.4; ^1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1 H), 8.84 (d, J = 5.63 Hz, 1 H), 8.32 - 8.27 (m, 1 H), 8.25 (d, J = 8.63 Hz, 1 H), 7.90 - 7.84 (m, 1 H), 7.79 (d, J = 7.63 Hz, 1 H), 7.14 (d, J = 5.63 Hz, 1 H), 4.54 - 4.43 (m, 1 H), 3.16 - 3.02 (m, 1 H), 2.80 - 2.68 (m, 1 H), 2.23 (s, 3 H), 2.07- 1.85 (m, 3 H), 1.82 - 1.73 (m, 1 H), 1.68 - 1.56 (m, 1 H), 1.55 - 1.40 (m, 1 H)
I-178	MS *m/z* 418.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.71(s, 1H), 8.85(d, J= 6.0Hz, 1H), 7.35(d, J= 6.4Hz, 1H), 7.30–7.25 (m, 2H), 6.65 (t, J= 73.6 Hz, 1H), 4.66–4.59 (m, 1H), 3.13–3.12 (m, 1H), 2.69 (s, 1H), 2.40 (d, J= 1.65 Hz, 3H), 2.35 (s, 3H), 2.34–2.15 (m, 2H), 2.07 (s, 1H), 1.89 (dd, J= 9.3, 4.1 Hz, 1H), 1.83–1.50 (m, 2H).
I-183	MS *m/z* 454.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.12 (dd, J = 4.4, 1.6 Hz, 1H), 7.91 (dd, J = 8.4, 1.6 Hz, 1H), 7.82 (dd, J = 8.4, 4.3 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.68 (s, 1H), 6.88 (t, J = 72.9 Hz, 1H), 4.59 – 4.48 (m, 1H), 3.12 (s, 1H), 2.84 – 2.62 (m, 1H), 2.59 – 2.32 (m, 5H), 2.15 – 1.99 (m, 1H), 1.98 – 1.85 (m, 1H), 1.83 – 1.62 (m, 2H).
I-184	MS *m/z* $[M+H]^+$: 418.4; ^1H NMR (400 MHz, DMSO-d6) δ 9.81 (s, 1 H), 8.83 (d, J=5.50 Hz, 1 H), 7.66 (d, J=7.50 Hz, 1 H), 7.52 - 7.35 (m, 3 H), 7.07 (d, J=5.50 Hz, 1 H), 4.51 - 4.39 (m, 1 H), 3.93 (s, 3 H), 3.16 – 2.98 (m, 1 H), 2.80 - 2.68 (m, 1 H), 2.22 (s, 3 H), 2.07 – 1.84 (m, 3 H), 1.81 - 1.71 (m, 1 H), 1.69 - 1.54 (m, 1 H), 1.52 - 1.38 (m, 1 H)
I-184	MS *m/z* 454.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.08 (dd, J = 4.4, 1.6 Hz, 1H), 8.78 (dd, J = 8.5, 1.6 Hz, 1H), 8.48 (s, 1H, formic acid), 7.89 (dd, J =

Compound	Spectral Data
	8.5, 4.4 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.59 (s, 1H), 6.85 (t, J = 73.5 Hz, 1H), 4.72 – 4.60 (m, 1H), 3.74 – 3.53 (m, 1H), 3.26 – 3.15 (m, 1H), 2.95 – 2.64 (m, 5H), 2.28 – 2.15 (m, 1H), 2.15 – 2.03 (m, 1H), 2.01 – 1.74 (m, 2H), NH not observed.
I-185	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.97 (s, 1H), 8.95 (d, J = 5.8 Hz, 1H), 8.54 (s, 1H, formic acid), 8.18 (d, J = 5.8 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.29 (s, 1H), 4.66 – 4.55 (m, 1H), 3.53 – 3.38 (m, 1H), 3.29 – 3.20 (m, 1H), 3.20 – 3.03 (m, 2H), 2.78 (s, 3H), 2.35 – 2.19 (m, 1H), 2.15 – 1.87 (m, 4H), 1.83 – 1.70 (m, 1H), NH and OH not observed
I-186	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.70 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 8.40 (s, 1H, formic acid), 7.57 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 4.70 – 4.58 (m, 1H), 3.82 – 3.69 (m, 1H), 3.65 – 3.54 (m, 1H), 3.53 – 3.43 (m, 1H), 3.42 – 3.33 (m, 1H), 3.03 (s, 3H), 2.40 – 2.27 (m, 1H), 2.25 – 2.13 (m, 1H), 2.12 – 1.95 (m, 3H), 1.89 – 1.72 (m, 1H), NH and OH not observed.
I-187	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.70 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.43 (s, 1H, formic acid), 7.57 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.4 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.28 (d, J = 1.7 Hz, 1H), 4.71 – 4.58 (m, 1H), 3.79 – 3.67 (m, 1H), 3.64 – 3.54 (m, 1H), 3.52 – 3.42 (m, 1H), 3.40 – 3.33 (m, 1H), 3.02 (s, 3H), 2.38 – 2.27 (m, 1H), 2.24 – 2.13 (m, 1H), 2.11 – 1.96 (m, 3H), 1.89 – 1.71 (m, 1H), NH and OH not observed
I-191	MS *m/z* 470.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 7.76 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.47 (s, 2H), 7.29 (t, J = 72.4 Hz, 1H), 7.26 (d, J = 5.6 Hz, 1H), 4.49-4.41 (m, 1H), 3.12-3.08 (m, 1H), 2.75-2.73 (m, 1H), 2.23 (s , 3H), 2.03-1.89 (m , 3H), 1.79-1.75 (m , 1H), 1.63-1.60 (m, 1H), 1.51-1.46 (m, 1H).
I-192	MS *m/z* 466.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.40 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.85-7.83 (m, 1H), 7.18 (d, J = 6.0 Hz, 1H), 4.52-4.48 (m, 1H), 3.39 (s, 3H), 3.30-3.27 (m, 1H), 3.20-3.17 (m, 1H), 2.83-2.78 (m, 1H), 2.35-2.29 (m , 3H), 2.08-2.00 (m , 2H), 1.83-1.80 (m, 1H), 1.67-1.63 (m, 1H), 1.55-1.53 (m, 1H).
I-198	MS *m/z* 386.0, 388.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.75 (s, 1H), 8.86 (d, J= 5.6Hz, 1H), 7.34 (s, 1H), 7.32–7.20 (m, 2H), 4.64 (s, 1H), 3.13 (s, 1H), 2.72 (s, 1H), 2.36 (s, 3H), 2.35–2.19 (m, 2H), 2.10 (s, 3H),1.96–1.83 (m, 1H), 1.88 (s,1H), 1.84–1.58 (m, 2H).
I-221	MS *m/z* 390.2, 392.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.97 (s, 1H), 8.95 (d, J= 5.6 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.40 (q, J = 10.4Hz,2.8 Hz,2H), 4.85-4.74 (m, 1H), 4.02 (d, J = 12 Hz, 1H), 3.59 (d, J = 12.4 Hz, 1H), 3.07-2.87 (m, 2H), 2.96 (s, 3H), 2.33 (d, J = 11.6 Hz, 1H), 2.19 (d, J = 14.8 Hz, 1H), 2.00-1.84(m, 2H).
I-222	MS *m/z* 420.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.77(s, 1H), 8.87(d, J= 5.6 Hz, 1H), 7.62(s, 1H), 7.51(d, J= 8.8Hz, 1H), 7.26 (d, J=5.6Hz, 1H), 4.65(s, 1H), 3.13-3.12(m, 1H), 2.71 (s, 1H), 2.36(s, 3H),2.32-2.23 (m, 2H),

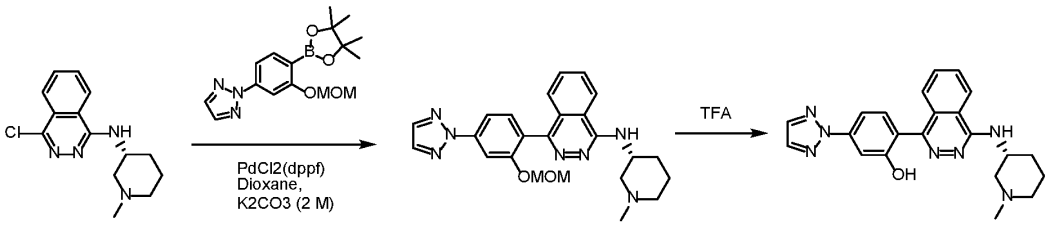
Compound	Spectral Data
	2.19(s, 3H), 2.10-2.09(m, 1H), 1.91-1.88(m, 1H), 1.82-1.63 (m, 2H), NH not observed
I-223	MS *m/z* 382.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.86 (s, 1H), 9.05 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 8.4, 2.2 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.71 – 7.59 (m, 2H), 4.69 (d, J = 12.4 Hz, 1H), 3.99 (d, J = 11.6 Hz, 1H), 3.61 (d, J = 12.4 Hz, 1H), 3.06 (d, J = 15.4 Hz, 1H), 2.98 (s, 3H), 2.35 (s, 1H), 2.20 (d, J = 14.8 Hz, 1H), 2.10 – 1.94 (m, 2H), 1.87 (d, J = 13.2 Hz, 1H), NH and OH not observed.
I-229	MS *m/z* 427.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.97 (s, 1H), 8.94 (d, J = 5.8 Hz, 1H), 8.49 (s, 1H, formic acid), 8.23 (dd, J = 5.8, 1.0 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 1.7 Hz, 1H), 7.05 (d, J = 16.3 Hz, 2H), 5.03 – 4.91 (m, 1H), 4.70 – 4.61 (m, 1H), 4.17 – 4.03 (m, 1H), 3.20 – 3.09 (m, 1H), 3.09 – 2.96 (m, 1H), 2.53 – 2.40 (m, 1H), 2.39 – 2.26 (m, 1H), NH and OH not observed.
I-231	MS *m/z* 440.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.99 (d, J = 5.8 Hz, 1H), 8.82 (s, 1H), 8.36 (d, J = 5.9 Hz, 1H), 8.31 (s, 1H), 7.84 (s, 2H), 7.74 (s, 1H), 7.61 (d, J = 8.25 Hz, 1H), 7.38 (t, J = 72.92 Hz, 1H), 4.45 – 4.31 (m, 1H), 3.33 – 3.25 (m, 1H), 2.95 (d, J = 12.1 Hz, 1H), 2.70 – 2.54 (m, 2H), 2.15 – 2.03 (m, 1H), 1.83 – 1.73 (m, 1H), 1.72 – 1.48 (m, 2H)
I-234	MS *m/z* 398.2 [M-H]-; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.72 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.42 - 7.31 (m, 3H), 7.13 - 6.70 (m, 1H), 4.71 - 4.61 (m, 1H), 3.79 (s, 3H), 2.88 (br s, 1H), 2.60 - 2.39 (m, 6H), 2.12 (br s, 1H), 2.02 - 1.91 (m, 1H), 1.91 - 1.65 (m, 2H); NH wasn't observed
I-236	MS *m/z* 443.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H, formic acid), 7.77 – 7.67 (m, 2H), 7.64 (s, 1H), 7.37 (t, J = 73.17 Hz, 1H), 6.19 (d, J = 8.50 Hz, 1H), 4.34 – 4.23 (m, 1H), 3.06 – 2.95 (m, 1H), 2.76 (t, J = 7.38 Hz, 2H), 2.73 – 2.68 (m, 3H), 2.23 (s, 3H), 2.06 – 1.84 (m, 5H), 1.79 – 1.68 (m, 1H), 1.65 – 1.50 (m, 1H), 1.46 – 1.31 (m, 1H)
I-239	MS *m/z* 404 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) d : 9.74 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 5.6 Hz, 1H), 6.75 (t, J = 55.2 Hz, 1H), 4.67 – 4.62 (m, 1H), 3.22 – 3.21 (m, 1H), 2.80 – 2.79 (m, 1H), 2.43 (s, 3H), 2.42 – 2.31 (m, 2H), 2.12 – 2.09 (m, 1H), 1.95 – 1.91 (m, 1H), 1.81 – 1.71 (m, 2H), NH not observed.
I-242	MS *m/z* 490.7 [M+H]+; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.73 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 2.4, 8.4 Hz, 1H), 6.66 (s, 1H), 4.77 - 4.60 (m, 1H), 3.87 (s, 3H), 3.47 - 3.36 (m, 1H), 3.05 - 2.92 (m, 1H), 2.58 (s, 5H), 2.24 - 2.10 (m, 1H), 2.07 - 1.97 (m, 1H), 1.93 - 1.72 (m, 2H), 1.58 - 1.42 (m, 1H), 0.81 - 0.67 (m, 2H), 0.67 - 0.50 (m, 2H); NH wasn't observed
I-245	MS *m/z* 375.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.53 (s, 1H, formic acid), 7.56 – 7.49 (m, 1H), 7.47 – 7.42 (m, 1H), 7.41 – 7.33 (m, 1H), 7.33 – 7.27 (m, 1H), 6.76 (t, J = 75.17 Hz, 1H), 4.51 – 4.42 (m, 1H), 3.57 – 3.41 (m, 1 H), 3.19 – 3.05 (m, 1 H), 2.88 (t, J = 7.3 Hz, 2H), 2.80 (t, J = 7.5 Hz,

Compound	Spectral Data
	2H), 2.76 - 2.60 (m, 5H), 2.14 (s, 4H), 1.92 – 1.76 (m, 1H), 1.76 – 1.60 (m, 1H). 1H not observed (NH)
I-249	MS *m/z* 388.7 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.78 (s, 1H), 8.93 (d, J = 5.6 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.55 - 7.44 (m, 1H), 7.13 - 6.77 (m, 1H), 4.80 - 4.66 (m, 1H), 3.51 (br d, J = 9.4 Hz, 1H), 3.20 - 3.02 (m, 1H), 2.78-2.75 (m, 2H), 2.67 (s, 3H), 2.21 - 2.14 (m, 1H), 2.13 - 2.03 (m, 1H), 1.95 - 1.77 (m, 2H); NH wasn't observed
I-250	MS *m/z* 409.4 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.56 (br s, 1H), 8.33 (d, J=2.4 Hz, 1H), 7.87 (br d, J=8.1 Hz, 1H), 7.12-7.31 (m, 2H), 4.34-4.60 (m, 1H), 3.59-3.88 (m, 1H), 3.28-3.44 (m, 1H), 2.92-3.07 (m, 1H), 2.82 (br s, 4H), 2.10 (m, 2H), 1.88 (m, 2H)
I-254	MS *m/z* 364.8 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.73 (s, 1H), 8.96 - 8.77 (m, 1H), 7.39 - 7.16 (m, 2H), 7.03 - 6.86 (m, 2H), 4.76 - 4.53 (m, 1H), 3.88 (s, 3H), 3.27 - 3.13 (m, 1H), 2.86 - 2.71 (m, 1H), 2.42 (s, 5H), 2.09 (s, 4H), 2.00 - 1.87 (m, 1H), 1.87 - 1.63 (m, 2H); NH wasn't observed
I-258	MS *m/z* 406.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 7.39 - 7.25 (m, 3 H), 6.02 (d, J = 7.75 Hz, 1 H), 4.30 - 4.19 (m, 1 H), 3.88 (s, 3 H), 3.01 – 2.90 (m, 1 H), 2.75 (t, J = 7.38 Hz, 2 H), 2.69 - 2.62 (m, 1 H), 2.55 (t, J = 7.75 Hz, 2 H), 2.20 (s, 3 H), 2.03 – 1.83 (m, 5 H), 1.74 - 1.66 (m, 1 H), 1.62 - 1.49 (m, 1 H), 1.42 – 1.29 (m, 1 H)
I-259	MS *m/z* 445.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1 H), 8.15 (d, J = 8.25 Hz, 1 H), 7.76 (d, J = 7.88 Hz, 1 H), 6.19 (d, J = 8.00 Hz, 1 H), 4.33 - 4.21 (m, 1 H), 2.96 (d, J = 9.01 Hz, 1 H), 2.77 (t, J = 7.44 Hz, 2 H), 2.70 - 2.64 (m, 1 H), 2.60 (t, J = 6.75 Hz, 2 H), 2.20 (s, 3 H), 2.01 (quin, J = 7.57 Hz, 2 H), 1.96 - 1.84 (m, 3 H), 1.70 (d, J = 3.63 Hz, 1 H), 1.63 - 1.49 (m, 1 H), 1.44 - 1.30 (m, 1 H)
I-265	MS *m/z* 440.5 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 9.53-9.79 (m, 1H), 8.76-9.01 (m, 1H), 7.60 (d, J=7.9 Hz, 1H), 7.51 (br d, J=5.4 Hz, 1H), 7.34 (d, J=7.9 Hz, 1H), 7.28 (s, 1H), 4.77-4.87 (m, 1H), 3.13-3.23 (m, 1H), 2.97 (q, J=10.1 Hz, 1H), 2.49-2.68 (m, 2H), 2.46 (s, 4H), 2.12-2.33 (m, 1H). NH and OH not observed.
I-267	MS *m/z* 380.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 9.56 (s, 1 H) 8.70 (br d, J=5.38 Hz, 1 H) 7.25 (d, J=5.50 Hz, 1 H) 6.40 (d, J=14.51 Hz, 2 H) 4.45 - 4.66 (m, 1 H) 3.54 (s, 3 H) 3.35 - 3.49 (m, 1 H) 2.94 - 3.09 (m, 1 H) 2.58 - 2.70 (m, 2 H) 2.28 (s, 3 H) 2.04 - 2.15 (m, 1 H) 1.90 - 2.01 (m, 1 H) 1.64 - 1.86 (m, 2 H)
I-268	MS *m/z* 366.1 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.40 (br s, 1H, formic acid peak), 9.56 (s, 1 H) 8.73 (br d, J=5.38 Hz, 1 H) 7.35 (d, J=5.63 Hz, 1 H) 6.26 (s, 2 H) 4.60 - 4.71 (m, 1 H) 3.52 - 3.75 (m, 1 H) 2.91 - 3.08 (m, 1 H) 2.65 - 2.87 (m, 2 H) 2.20 (s, 3 H) 2.06 - 2.15 (m, 1 H) 1.88 - 2.00 (m, 1 H) 1.63 - 1.84 (m, 2 H). NH and OH not observed
I-287	MS *m/z* 400.3 $[M+H]^-$; ^{1}H NMR (400 MHz, DMSO–d6) d: 9.81(s, 1H), 8.86(d, J= 4.0Hz, 1H), 7.67(d, J= 8.0Hz, 1H), 7.45–7.43(m, 1H), 7.32–7.31(m, 1H), 7.28–7.26(m, 1H),7.24–7.23(m, 1H),6.85(t, J= 110.0 Hz, 1H), 4.49–4.46(m,

Compound	Spectral Data
	1H), 3.91(s, 3H), 3.12–3.09(m, 1H), 2.75–2.72(m, 1H), 2.23(s, 3H), 2.04–1.91(m, 3H), 1.77–1.75(m, 1H),1.64–1.60(m, 1H),1.50–1.45(m, 1H).
I-290	MS *m/z* 400.0 $[M-H]^-$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.77 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.70 (br d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 5.6 Hz, 1H), 4.66 (td, J = 4.4, 8.4 Hz, 1H), 3.15 (br s, 1H), 2.72 (br s, 1H), 2.38 (s, 5H), 2.23 - 2.19 (m, 3H), 2.16 - 2.04 (m, 1H), 1.97 - 1.86 (m, 1H), 1.85 - 1.62 (m, 2H); NH wasn't observed
I-291	MS *m/z* 446.8 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.73 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.41 - 7.36 (m, 1H), 4.78 - 4.60 (m, 2H), 3.15 (br s, 1H), 2.72 (br s, 1H), 2.45 - 2.24 (m, 5H), 2.11 (br s, 1H), 1.98 - 1.85 (m, 1H), 1.85 - 1.60 (m, 2H), 1.19 - 1.06 (m, 6H); NH wasn't observed
I-296	MS *m/z* 392.5 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 9.73 (s, 1H), 8.84 (d, J=5.8 Hz, 1H), 7.30 (d, J=5.5 Hz, 1H), 7.19 (d, J=8.3 Hz, 1H), 7.07 (s, 1H), 6.94 (dd, J=8.5, 1.9 Hz, 1H), 4.60-4.71 (m, 1H), 3.90 (s, 3H), 3.10-3.26 (m, 1H), 2.65-2.85 (m, 1H), 2.54-2.65 (m, 1H), 2.41 (s, 3H), 2.30-2.38 (m, 1H), 2.03-2.21 (m, 1H), 1.59-1.95 (m, 3H), 1.16 (d, J=6.7 Hz, 3H), 1.08 (d, J=6.7 Hz, 3H). NH and OH not observed.
I-299	MS *m/z* 384.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 9.73 (s, 1 H), 8.89 (br d, J=5.63 Hz, 1 H), 8.40 (br s, 1 H, formic acid), 7.69 (s, 1 H), 7.54 (br d, J=7.88 Hz, 1 H), 7.37 (d, J=6.50 Hz, 2 H), 6.69 (t, J=54.66 Hz, 1 H), 4.79 - 4.65 (m, 1 H), 3.93 - 3.73 (m, 1 H), 3.50 - 3.35 (m, 1 H), 3.15 - 2.95 (m, 2 H), 2.89 (s, 3 H), 2.54 (s, 3 H), 2.33 - 2.12 (m, 2 H), 2.02 - 1.84 (m, 2 H). 1H not observed (NH)
I-316	MS *m/z* 391.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.72 (s, 1H), 8.87 (s, 1H), 7.69 – 7.42 (m, 2H), 7.39 – 7.16 (m, 2H), 4.85 – 4.75 (m, 1H), 2.74 – 2.60 (m, 2H), 2.37 – 2.20 (m, 2H), 1.45 (s, 3H), NH and 2 OHs not observed.
I-319	MS *m/z* 454.3 $[M+H]^+$; ^1H NMR (400MHz, Chloroform-d) δ 9.52 (s, 1H), 8.94 (d, J=5.6 Hz, 1H), 8.07 (s, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.67 (d, J=5.6Hz, 1H), 7.51 (d, J=8.4Hz, 1H), 6.98 (t, J=54.8 Hz, 1H), 6.66 (s, 1H), 4.81–4.80 (m, 1H), 2.82–2.80 (m, 2H), 2.55–2.52 (m, 1H), 2.35 (s, 3H), 2.20–2.10 (m, 2H), 1.91–1.81 (m, 1H), 1.67–1.63 (m, 2H).
I-320	MS *m/z* 454.3 $[M+H]^+$; ^1H NMR (400 MHz, Chloroform-d) d: 9.55 (s,1H), 8.88 (d, J = 5.6 Hz, 1H), 7.72 (s, 1H), 7.46 (s, 2H), 7.31 (d, J = 5.6 Hz, 1H), 6.95 (t, J = 55.2 Hz, 1H), 6. 81 (s, 1H), 4.83 – 4.82 (m, 1H), 2.89 – 2.83(m, 2H), 2.56 – 2.53 (m, 1H), 2.37 (s, 3H), 2.22 – 2.07 (m, 2H),1.92 – 1.89 (m, 1H), 1.69 – 1.68 (m, 2H).

Example 3

Preparation of Compound I-10



Step 1. (R)-4-(2-(Methoxymethoxy)-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

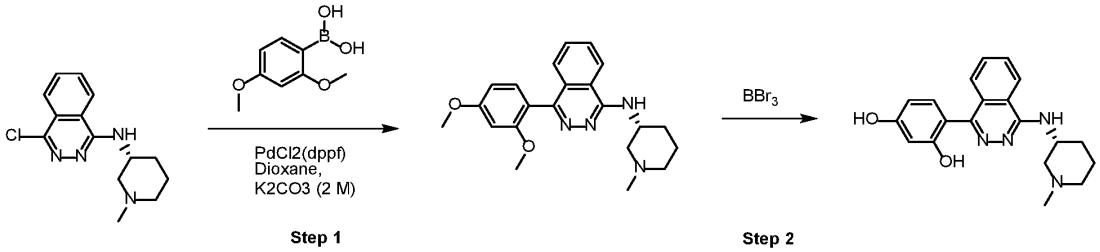
To a solution of (R)-4-chloro-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (Intermediate 19a, 100 mg, 0.36 mmol) in 1.5 mL 1,4-dioxane and 0.3 mL water was added 2-(3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2H-1,2,3-triazole (119 mg, 0.36 mmol, 1.0 eq), K_2CO_3 (100mg, 0. 72 mmol, 2.0 eq) and $Pd(dppf)Cl_2$ (40 mg, 0.15 eq). This mixture was stirred at 90 °C under N_2 for 16 h before concentration. The residue was purified by flash column chromatography (DCM/MeOH = 17:3) to give (R)-4-(2-(methoxymethoxy)-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (124 mg, 76%) as brown oil. MS *m/z* 446.2 $[M+H]^+$.

Step 2. (R)-2-(4-((1-Methylpiperidin-3-yl)amino)phthalazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol

A solution of (R)-4-(2-(methoxymethoxy)-4-(2H-1,2,3-triazol-2-yl)phenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (124 mg, 0.28 mmol) in 1 mL TFA was stirred at 25 °C for 3 h before concentration. The residue was mixed with 5 mL water, basified with sat. $NaHCO_3$ to pH = 8, and extracted with DCM (10 mL × 3). The combined DCM was dried over Na_2SO_4, concentrated, and purified by flash column chromatography [DCM/NH_3 (7 M in MeOH) = 10:1] to give (R)-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol (74 mg, 72%) as brown foam. MS *m/z* 402.2 $[M+H]^+$; ^1H NMR (DMSO-d_6) δ: 10.28 (s, 1H), 8.40 (d, J = 8.2 Hz, 1H), 8.16 (s, 2H), 7.86 (t, J = 7.6 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 8.2, 2.1 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 4.52 – 4.36 (m, 1H), 3.19 – 3.03 (m, 1H), 2.81 – 2.69 (m, 1H), 2.24 (s, 3H), 2.04 – 1.89 (m, 3H), 1.83 – 1.72 (m, 1H), 1.70 – 1.56 (m, 1H), 1.53 – 1.42 (m, 1H).

Example 4

Preparation of Compound I-15



Step 1. (R)-4-(2,4-Dimethoxyphenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

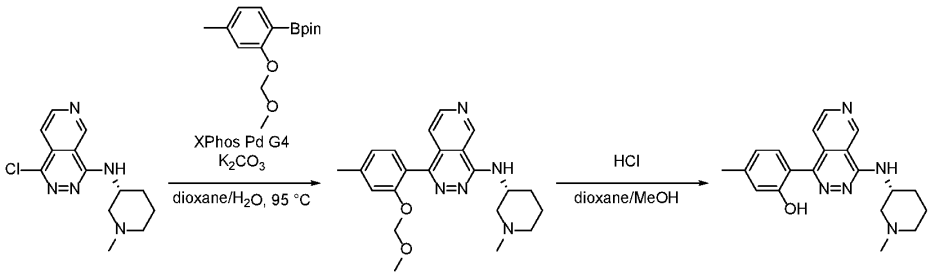
To a solution of (R)-4-chloro-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (Intermediate 19a, 185 mg, 0.67 mmol) in 1 mL 1,4-dioxane and 0.2 mL water was added (2,4-dimethoxyphenyl)boronic acid (182mg, 1.0 mmol, 1.5 eq), K_2CO_3 (185mg, 1.34 mmol, 2.0 eq) and $Pd(dppf)Cl_2$ (73mg, 0.1 mmol, 0.15 eq). This mixture was stirred at 90 °C under N_2 for 16 h before concentration. The residue was purified by flash column chromatography (DCM/MeOH = 10:1) to give (R)-4-(2,4-dimethoxyphenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (200 mg, 79%) as brown solid. MS *m/z* 379.1 $[M+H]^+$.

Step 2. (R)-4-(4-((1-Methylpiperidin-3-yl)amino)phthalazin-1-yl)benzene-1,3-diol

To a solution of (R)-4-(2,4-dimethoxyphenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine (120 mg, 0.31 mmol) in 1.5 mL DCM was added BBr_3 (1 M in DCM, 2.2 mL, 2.2 mmol, 7 eq). The mixture was stirred at RT for 3 h then diluted with MeOH (3 ml), stirred for another 30 min and concentrated. The residue was purified by flash column chromatography [DCM/NH_3(7 M in MeOH) = 20:1] and prep-TLC (DCM/Et_3N (0.07 M in MeOH)) to give (R)-4-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)benzene-1,3-diol (45 mg, 40%) as white solid. MS *m/z* 351.1 $[M+H]^+$; ^1H NMR (MeOD-d4) δ: 8.25 (d, J = 8.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.80 – 7.72 (m, 2H), 7.21 – 7.14 (m, 1H), 6.48 – 6.46 (m, 2H), 4.62 – 4.48 (m, 1H), 3.47 (q, J = 7.3 Hz, 1H), 3.15 – 3.05 (m, 1H), 2.73 – 2.60 (m, 1H), 2.40 – 2.60 (m, 4H), 2.08 – 1.98 (m, 1H), 1.90 – 1.80 (m, 1H), 1.78 – 1.68 (m, 1H), 1.68 – 1.55 (m, 1H).

Example 5

Preparation of Compound I-71



Step 1: 1-[2-(Methoxymethoxy)-4-methyl-phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrido[3,4-*d*]pyridazin-4-amine

1-Chloro-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (Intermediate 20a, 0.50 g, 1.80 mmol), [2-(methoxymethoxy)-4-methyl-phenyl]boronic acid (prepared according to the procedure of Intermediate 5a, 0.46 g, 2.34 mmol), and XPhos Pd G4 (0.098 g, 0.108 mmol) were added to a vial and evacuated and refilled with Ar. The mixture was dissolved in dioxane (9.0 mL) and K_2CO_3 (2 M, 2.7 mL, 5.40 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 2.5 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 10%) gave an dark-yellow foam (0.596 g, 80%). MS *m/z* 394.1 $[M+H]^+$.

Step 2. 5-Methyl-2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrido[3,4-*d*]pyridazin-1-yl]phenol

1-[2-(Methoxymethoxy)-4-methyl-phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrido[3,4-*d*]pyridazin-4-amine (1.19 g, 3.02 mmol) in MeOH (2 mL) was added HCl/dioxane (4M, 4.0 mL) and stirred for 2 h. The reaction was concentrated and then dissolved in DCM/iPrOH (9:1). The solution was washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated to give a light-yellow solid (0.905 g, 86%). MS *m/z* 350.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.61 (s, 1H), 8.83 (d, *J* = 5.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 5.6 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.81 (s, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 4.52 – 4.34 (m, 1H), 3.10 (d, *J* = 7.9 Hz, 1H), 2.72 (d, *J* = 10.4 Hz, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 2.07 – 1.98 (m, 1H), 1.97 – 1.86 (m, 2H), 1.82 – 1.72 (m, 1H), 1.68 – 1.54 (m, 1H), 1.52 – 1.39 (m, 1H).

The compounds below were prepared according to the procedure of Example 5 by

substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-14	MS *m/z* 353.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 9.91 (s, 1H), 8.41 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.34 (q, J = 7.8, 7.3 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.79 (t, J = 8.7 Hz, 1H), 4.49 – 4.37 (m, 1H), 3.16 – 3.02 (m, 1H), 2.72 (d, J = 10.9 Hz, 1H), 2.23 (s, 3H), 1.96 (q, J = 10.8, 9.4 Hz, 3H), 1.76 (dd, J = 10.3, 6.0 Hz, 1H), 1.62 (q, J = 12.3 Hz, 1H), 1.48 (tt, J = 13.2, 6.4 Hz, 1H).
I-16	MS *m/z* 353.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 10.17 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 7.84 (t, J = 7.4 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.11 – 7.03 (m, 1H), 6.83 – 6.75 (m, 2H), 4.45 – 4.35 (m, 1H), 3.15 – 3.05 (m, 1H), 2.78 – 2.74 (m, 1H), 2.22 (s, 3H), 2.05 – 1.90 (m, 3H), 1.80 – 1.73 (m, 1H), 1.65 – 1.57 (m, 1H), 1.53 – 1.45 (m, 1H).
I-17	MS *m/z* 349.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.28 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.87 (d, J = 8.0 Hz, 1H), 4.64 – 4.53 (m, 1H), 3.27 – 3.04 (m, 2H), 2.85 – 2.68 (m, 1H), 2.50 – 2.35 (m, 4H), 2.32 (s, 3H), 2.13 – 2.00 (m, 1H), 1.97 – 1.85 (m, 1H), 1.86 – 1.74 (m, 1H), 1.73 – 1.59 (m, 1H), NH and OH not observed.
I-18	MS *m/z* 367.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ: 8.27 (d, J = 8.0 Hz, 1H), 7.90 – 7.74 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.61 – 4.52 (m, 1H), 3.26 – 3.06 (m, 1H), 2.73 (s, 1H), 2.39 (s, 3H), 3.35 – 2.15(m, 2H), 2.30 (t, J = 1.6 Hz, 3H), 2.13 – 1.99 (m, 1H), 1.93 – 1.84 (m, 1H), 1.83 – 1.64 (m, 2H), NH and OH not observed.
I-24	MS *m/z* 360.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.46 (d, J = 4.6 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.89 – 7.75 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.33 (d, J = 1.2 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 4.49 – 4.36 (m, 1H), 3.09 (d, J = 7.6 Hz, 1H), 2.72 (d, J = 10.0 Hz, 1H), 2.22 (s, 3H), 2.02 – 1.88 (m, 3H), 1.80 – 1.70 (m, 1H), 1.67 – 1.54 (m, 1H), 1.53 – 1.40 (m, 1H).
I-25	MS *m/z* 349.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.28 (d, J = 8.0 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.81 – 7.75 (m, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.87 – 6.80 (m, 2H), 4.62 – 4.53 (m, 1H), 3.35 – 3.18 (m, 1H), 3.24 – 3.08 (m, 2H), 2.80 – 2.71 (m, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.11 – 2.01 (m, 1H), 1.95 – 1.86 (m, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.62 (m, 1H), NH and OH not observed.
I-27	MS *m/z* 349.1 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.31 (d, J=8.0 Hz, 1H), 7.88 (ddd, J=8.2, 5.0, 3.4 Hz, 1H), 7.78-7.84 (m, 2H), 7.16-7.31 (m, 2H), 6.92 (t, J=7.5 Hz, 1H), 4.56 (dt, J=8.3, 4.4 Hz, 1H), 3.01-3.24 (m, 1H), 2.69 (br dd, J=3.5, 1.5 Hz, 1H), 2.27-2.45 (m, 8H), 1.98-2.11 (m, 1H), 1.83-1.93 (m, 1H), 1.64-1.83 (m, 2H), NH and OH not observed.
I-28	MS *m/z* 353.1 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.29 (d, J=8.2 Hz, 1H), 7.87 (t, J=7.3 Hz, 1H), 7.76-7.82 (m, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.24 (ddd, J=10.9, 8.3, 1.6 Hz, 1H), 7.14 (d, J=7.3 Hz, 1H), 6.97 (td, J=7.9, 4.8 Hz, 1H), 4.59 (dt, J=8.6, 4.4 Hz, 1H), 3.13-3.28 (m, 1H), 2.66-2.88 (m, 1H), 2.35-2.49

Compound	Spectral Data
	(m, 5H), 2.00-2.12 (m, 1H), 1.85-1.96 (m, 1H), 1.64-1.83 (m, 2H), NH and OH not observed.
I-50	MS *m/z* 349.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.30 (d, *J* = 8.3 Hz, 1H), 7.87 (t, 7.2 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 4.63-4.60 (m, 1H), 3.30 – 3.25 (m, 1H), 2.88-2.84 (m, 1H), 2.48-2.40 (m, 5H), 2.12-2.08 (m, 1H), 1.97-1.92 (m, 4H), 1.87 – 1.63 (m, 2H), NH and OH not observed.
I-51	MS *m/z* 367.0 $[M+H]^+$; ^1H NMR (METHANOL-d_4) δ: 8.27 (d, J=8.3 Hz, 1H), 7.85 (t, J=7.2 Hz, 1H), 7.76-7.81 (m, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.02 (dd, J=7.8, 1.3 Hz, 1H), 6.84 (t, J=7.4 Hz, 1H), 4.59 (dt, J=8.7, 4.5 Hz, 1H), 3.24-3.29 (m, 1H), 2.74-2.91 (m, 1H), 2.45 (m, 5H), 2.35 (d, J=2.0 Hz, 3H), 2.07 (m, 1H), 1.86-1.98 (m, 1H), 1.67-1.86 (m, 2H), NH and OH not observed.
I-41	MS *m/z* 363.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.25 (d, 1H), 7.86 – 7.80 (m, 1H), 7.78 – 7.72 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.08 (s, 1H), 6.78 (s, 1H), 4.62 – 4.50 (m, 1H), 3.21 – 3.07 (m, 1H), 2.77 – 2.63 (m, 1H), 2.37 (m, 5H), 2.29 (s, 3H), 2.23 (s, 3H), 2.09 – 2.02 (m, 1H), 1.93 – 1.83 (m, 1H), 1.82 – 1.57 (m, 2H), NH and OH not observed.
I-42	MS *m/z* 363.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.09 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.98 – 7.66 (m, 3H), 7.14 (d, J = 7.6 Hz, 2H), 6.82 (d, J = 7.6 Hz, 1H), 4.49 – 4.36 (m, 1H), 3.12 – 3.04 (m, 1H), 2.76 – 2.66 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.06 – 1.85 (m, 3H), 1.80 – 1.71 (m, 1H), 1.68 – 1.56 (m, 1H), 1.53 – 1.43 (m, 1H).
I-56	MS *m/z* 417.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.37 – 8.24 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.30 – 6.22 (m, 1H), 4.82 – 4.61 (m, 1H), 4.45 – 4.27 (m, 2H), 3.96 (t, J = 8.0 Hz, 2H), 2.90 – 2.61 (s, 2H), 2.60 – 2.48 (m, 2H), 2.33 (s, 3H), 2.20 – 2.03 (m, 2H), 1.90 – 1.76 (m, 3H), 1.71 – 1.55 (m, 3H).
I-57	MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.91 – 7.83 (td, J = 12.0, 4.0 Hz, 1H), 7.81 (td, J = 12.0, 4.0 Hz, 1H),7.59 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 1.6 Hz, 1H), 6.99 (dd, J = 8.0, 1.6 Hz, 1H), 6.40 (s, 1H), 6.35 – 6.29 (m, 1H), 5.05 (td, J = 4.8, 2.0 Hz, 2H), 4.88 (m, 2H), 4.76 – 4.68 (m, 1H), 2.95 – 2.75 (m, 2H), 2.51 (m, 1H), 2.34 (s, 3H), 2.13 (m, 2H), 1.84 (m, 1H), 1.70 – 1.51 (m, 2H).
I-61	MS *m/z* 405.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.27 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.98 – 6.89 (m, 2H), 4.72 – 4.60 (m, 1H), 4.17 – 4.02 (m, 2H), 3.98 – 3.87 (m, 1H), 3.76 (t, J = 7.6 Hz, 1H), 3.57 – 3.38 (m, 2H), 3.09 – 2.97 (m, 1H), 2.87 – 2.69 (m, 2H), 2.60 (s, 3H), 2.46 – 2.37 (m, 1H), 2.20 – 2.10 (m, 1H), 2.10 – 1.97 (m, 2H), 1.88 – 1.69 (m, 2H).
I-72	MS *m/z* 354.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.81 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.77 – 7.63 (m, 1H), 7.37 (dd, J = 15.2, 8.4 Hz, 1H), 7.18 (d, J = 5.6 Hz, 1H), 6.92 – 6.76 (m, 2H), 4.56 – 4.45 (m, 1H), 3.23 –

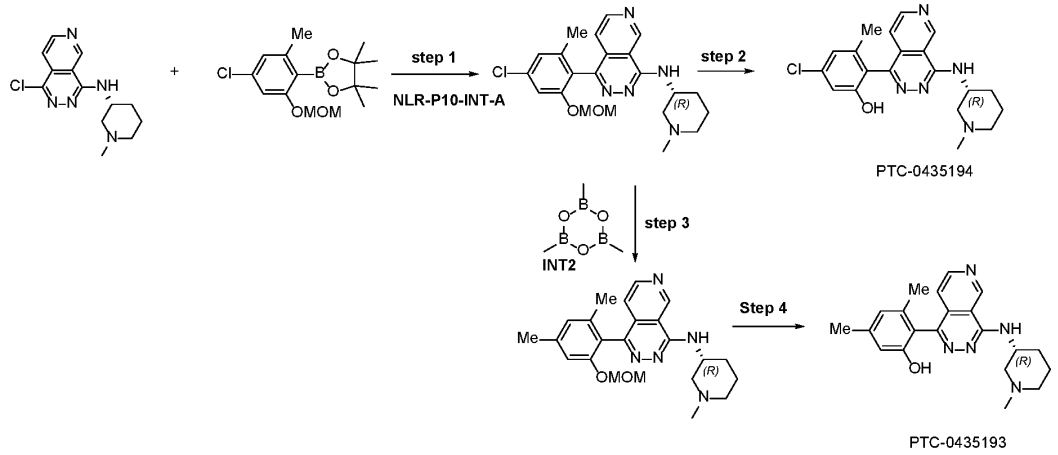
Compound	Spectral Data
	3.12 (m, 1H), 2.86 – 2.78 (m, 1H), 2.31 (s, 3H), 2.15 – 1.97 (m, 3H), 1.88 – 1.76 (m, 1H), 1.70 – 1.60 (m, 1H), 1.57 – 1.44 (m, 1H).
I-74	MS *m/z* 361.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 8.38 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 7.85 (t, J = 7.2 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 4.55 – 4.43 (m, 1H), 3.31 – 3.20 (m, 1H), 2.95 – 2.85 (m, 1H), 2.41 (s, 3H), 2.31 – 2.19 (m, 2H), 2.03 – 1.95 (m, 1H), 1.88 – 1.77 (m, 1H), 1.73 – 1.46 (m, 2H).
I-75	MS *m/z* 404.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.13 (d, J = 7.2 Hz, 1H), 7.77 – 7.64 (m, 3H), 7.52 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 4.55 – 4.36 (m, 1H), 3.18 – 3.07 (m, 1H), 2.81 – 2.64 (m, 1H), 2.50 – 2.42 (m, 1H), 2.38 (s, 3H), 2.00 – 1.90 (m, 1H), 1.89 – 1.76 (m, 1H), 1.76 – 1.53 (m, 2H), 1.27 – 1.12 (m, 1H).
I-78	MS *m/z* 351.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ： 11.99 (s, 1H), 9.74 (s, 1H), 8.83 (d, J = 4.0 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.42 – 7.36 (m, 1H), 6.23 – 6.17 (m, 1H), 4.51 – 4.34 (m, 1H), 3.14 – 3.04 (m, 1H), 2.80 – 2.69 (m, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 2.05 – 1.89 (m, 3H), 1.82 – 1.72 (m, 1H), 1.69 – 1.54 (m, 1H), 1.52 – 1.39 (m, 1H).
I-79	MS *m/z* 404.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.24 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 7.87 – 7.77 (m, 2H), 7.73 – 7.69 (m, 1H), 7.01 (s, 1H), 4.76 – 4.64 (m, 1H), 3.63 (s, 1H), 3.19 (s, 1H), 2.95 – 2.80 (m, 2H), 2.70 (s, 3H), 2.25 – 2.16 (m, 1H), 2.12 – 2.03 (m, 1H), 2.00 – 1.88 (m, 1H), 1.84 – 1.72 (m, 1H).
I-80	MS *m/z* 361.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.12 (d, J = 6.4 Hz, 1H), 7.76 – 7.66 (m, 3H), 7.63 – 7.57 (m, 1H), 7.15 (d, J = 7.2 Hz, 1H), 4.64 – 4.56 (m, 1H), 3.40 – 3.32 (m, 1H), 3.03 – 2.93 (m, 1H), 2.90 – 2.68 (m, 2H), 2.59 (s, 3H), 2.08 – 1.94 (m, 2H), 1.86 – 1.68 (m, 2H);
I-82	MS *m/z* 350.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.92 (d, J = 5.7 Hz, 1H), 7.99 (d, J = 5.7 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.24 – 7.14 (m, 2H), 6.91 (t, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.79 – 4.68 (m, 1H), 3.03 – 2.77 (m, 2H), 2.70 – 2.54 (m, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 2.30 – 2.21 (m, 1H), 2.16 – 2.01 (m, 1H), 1.99 – 1.87 (m, 1H), 1.74 – 1.61 (m, 2H).
I-86	MS *m/z* 350.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.10 (dd, J = 4.4, 1.7 Hz, 1H), 8.50 (s, 1H), 8.09 (dd, J = 8.3, 1.7 Hz, 1H), 7.82 (dd, J = 8.5, 4.4 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 6.89 – 6.81 (m, 2H), 4.64 – 4.50 (m, 1H), 3.67 – 3.49 (m, 1H), 3.24 – 3.08 (m, 1H), 3.02 – 2.78 (m, 2H), 2.73 (s, 3H), 2.39 (s, 3H), 2.25 – 2.02 (m, 2H), 1.98 – 1.74 (m, 2H)
I-88	MS *m/z* 368.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 9.65 (s, 1H), 8.79 (d, J = 5.7 Hz, 1H), 7.53 (d, J = 5.6 Hz, 1H), 7.02 (d, J = 9.7 Hz, 1H), 6.78 (d, J = 6.5 Hz, 1H), 4.62 – 4.51 (m, 1H), 3.19 – 2.99 (m, 1H), 2.71 – 2.58 (m, 1H), 2.32 (s, 3H), 2.29 – 2.13 (m, 5H), 2.08 – 2.00 (m, 1H), 1.89 – 1.80 (m, 1H), 1.78 – 1.54 (m, 2H).
I-94	MS *m/z* 414.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ: 8.38 (d, J = 8.0 Hz, 1H), 7.85 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.79 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.17 (t, *J* = 2.0 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.77 (t, *J* = 2.4 Hz, 1H), 6.38 (dd, *J* = 2.8, 1.8 Hz, 1H),

Compound	Spectral Data
	4.49 – 4.38 (m, 1H), 3.18 – 3.11 (m, 1H), 2.82 – 2.72 (m, 1H), 2.28 (s, 3H), 2.09 – 1.94 (m, 3H), 1.83 – 1.74 (m, 1H), 1.70 – 1.57 (m, 1H), 1.55 – 1.43 (m, 1H).
I-92	MS *m/z* 360.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.60 (s, 1H), 8.74 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 5.7 Hz, 1H), 7.25 (dd, J = 7.8, 1.4 Hz, 1H), 7.18 (d, J = 1.4 Hz, 1H), 4.59 – 4.46 (m, 1H), 3.15 – 3.00 (m, 1H), 2.72 – 2.59 (m, 1H), 2.34 – 2.20 (m, 5H), 2.07-2.04 (m, 1H), 1.86 – 1.76 (m, 1H), 1.76 – 1.48 (m, 2H).
I-123	MS *m/z* 402.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ: 8.35 (d, J = 9.38 Hz, 1 H), 8.30 (s, 1 H, formic acid), 7.95 (t, J = 7.63 Hz, 1 H), 7.87 (t, J = 8.00 Hz, 1 H), 7.68 (d, J = 8.13 Hz, 1 H), 7.30 (d, J = 7.88 Hz, 1 H), 7.18 (s, 1 H), 7.05 (d, J = 8.00 Hz, 1 H), 4.74 – 4.63 (m, 1 H), 3.97 – 3.78 (m, 1 H), 3.51 - 3.38 (m, 2 H), 3.19 – 2.98 (m, 2 H), 2. 90 (s, 3 H), 2.13 - 2.34 (m, 2 H), 1.80 - 2.07 (m, 1 H). 3Hs not observed (3 NH)
I-122	MS *m/z* 454.2 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ: 9.00 (d, J = 5.63 Hz, 1 H), 8.90 (s, 1 H), 8.38 (s, 1 H, formic acid), 8.26 (d, J = 5.63 Hz, 1 H), 7.88 – 7.77 (m 2 H), 7.73 (s, 1 H), 6.96 (td, J = 73.04 Hz, 8.75 Hz, 1 H), 4.77 – 4.67 (m, 1 H), 3.87 - 3.72 (m, 1 H), 3.46 – 3.37 (m, 1 H), 3.16 - 2.97 (m, 2 H), 2.88 (s, 3 H), 2.32 - 2.12 (m, 2 H), 2.05 – 1.83 (m, 2 H); 1H not observed (NH)
I-99	MS *m/z* 350.2 $[M+H]^+$; ^1H NMR (MeOH-d4) d: 8.99 (s, 1H), 8.90 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 5.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.86 (s, 1H), 4.51-4.63 (m, 1H), 3.20-3.30 (m, 1H), 2.75-2.85 (m, 1H), 2.38-2.49 (m, 8H), 2.05-2.15 (m, 1H), 1.90-1.97 (m, 1H), 1.65-1.87 (m, 2H). Two exchangeable protons are not seen.
I-125	MS *m/z* 416.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ: 8.42 (d, J = 8.13 Hz, 1 H), 8.18 (s, 1 H, formic acid), 7.86 (t, J = 8.50 Hz, 1 H), 7.77 (t, J = 7.63 Hz, 1 H), 7.39 (d, J = 8.25 Hz, 1 H), 7.26 (d, J = 7.63 Hz, 1 H), 7.21 - 7.13 (m, 1 H), 7.01 (d, J = 7.75 Hz, 1 H), 6.87 (s, 1 H), 5.48 (d, J = 4.88 Hz, 1 H), 4.54 - 4.40 (m, 1 H), 3.18 – 3.08 (m, 1 H), 2.83 – 2.73 (m, 1 H), 2.66 (d, J = 4.63 Hz, 3 H), 2.26 (s, 3 H), 2.05 – 1.92 (m, 3 H), 1.84 - 1.72 (m, 1 H), 1.68 - 1.55 (m, 1 H), 1.55 - 1.40 (m, 1 H).
I-102	MS *m/z* 420.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ：10.38 (s, 1H), 9.78 (s, 1H), 8.85 (d, J = 4.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.29 (dd, J = 5.6, 0.6 Hz, 1H), 7.00 – 6.92 (m, 2H), 4.53 – 4.40 (m, 1H), 3.20 – 3.08 (m, 1H), 2.84 – 2.69 (m, 1H), 2.26 (s, 3H), 2.07 – 1.90 (m, 3H), 1.84 – 1.73 (m, 1H), 1.70 – 1.56 (m, 1H), 1.55 – 1.39 (m, 1H);
I-103	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.72 (d, J = 0.7 Hz, 1H), 8.80 (d, J = 5.6 Hz, 1H), 7.28 (d, J = 5.6 Hz, 1H), 7.20 (s, 1H), 7.08 (s, 1H), 4.68 – 4.60 (m, 1H), 3.28 – 3.16 (m, 1H), 2.84 – 2.72 (m, 1H), 2.45-2.30 (m, 5H), 2.15-2.08 (m, 4H), 1.96 – 1.88 (m, 1H), 1.83 – 1.68 (m, 2H).
I-105	MS *m/z* 350.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ： 9.70 (s, 1H), 8.77 (t, J = 14.2 Hz, 1H), 7.28 (d, J = 5.6 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.70 – 4.53 (m, 1H), 3.24 – 3.09 (m,

Compound	Spectral Data
	1H), 2.79 – 2.64 (m, 1H), 2.50 – 2.23 (m, 5H), 2.15 – 2.04 (m, 1H), 2.00 (s, 3H), 1.94 – 1.83 (m, 1H), 1.83 – 1.59 (m, 2H).
I-182	MS *m/z* 431.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 9.52 (s, 1H), 8.72 (d, J=5.6 Hz, 1H), 8.06 (s, 1H), 7.83-7.99 (m, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.29 (d, J=5.6 Hz, 1H), 4.51-4.68 (m, 1H), 3.59-3.77 (m, 1H), 3.28 (br s, 1H), 3.15-3.24 (m, 3H), 2.97 (br s, 1H), 2.71-2.76 (m, 1H), 2.07-2.15 (m, 1H), 2.04 (br s, 1H), 1.68-1.95 (m, 2H).
I-190	MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 9.77 (s, 1H), 8.91 (d, J=5.6 Hz, 1H), 8.37 (s, 1H), 8.06 (s, 1H), 7.82 (d, J=7.9 Hz, 1H), 7.60 (d, J=7.9 Hz, 1H), 7.39 (dd, J=5.8, 0.9 Hz, 1H), 4.69-4.84 (m, 1H), 4.53 (br s, 2H), 3.83 (br d, J=9.0 Hz, 1H), 3.44 (br d, J=11.5 Hz, 1H), 3.03-3.18 (m, 2H), 2.92 (s, 3H), 2.15-2.32 (m, 2H), 1.89-2.08 (m, 2H)
I-197	MS *m/z* 421.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 7.73 (d, J = 7.2 Hz, 1 H), 7.26 (d, J = 8.8 Hz, 1H), 7.23 (d, J= 5.6 Hz, 1H), 7.15 (s, 1H), 4.49-4.45 (m, 1H), 3.10 (d, J = 8.8 Hz, 1H), 2.74-2.71 (m, 1H), 2.23 (s, 3H), 2.04-1.90 (m, 3H), 1.79-1.76 (m, 1H), 1.66-1.57 (m, 1H), 1.52-1.45 (m, 1H)
I-220	MS *m/z* 415 $[M-H]^-$; ^1H NMR (400 MHz, DMSO–d6) δ 9.92 (br s, 1H), 8.41 (dd, J = 11.6, 8.4 Hz, 1H), 8.24 (s, 1H, formic acid), 7.90 (q, J = 7.2 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.70 – 7.59 (m, 2H), 7.49 – 7.45 (m, 2H), 7.31 – 7.20 (m, 2H), 4.61 – 4.59 (br s, 1H), 3.58 – 3.55 (m, 1H), 3.24 – 3.21 (m, 1H), 2.94 – 2.88 (m, 2H), 2.13 – 2.11 (m, 1H), 1.99 – 1.96 (m, 1H), 1.80 – 1.78 (m, 2H).
I-273	MS *m/z* 398.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.88 (br s, 1 H), 9.78 (s, 1 H), 8.84 (d, J = 5.63 Hz, 1 H), 8.16 (s, 1 H, formic acid), 7.61 (d, J = 7.50 Hz, 1 H), 7.17 (d, J = 5.50 Hz, 1 H), 6.70 - 6.61 (m, 2 H), 4.57 - 4.34 (m, 1 H), 3.53 (t, J = 7.00 Hz, 2 H), 3.22 - 3.14 (m, 1 H), 2.84 (d, J = 11.26 Hz, 1 H), 2.49 - 2.44 (m, 3 H), 2.33 (s, 3 H), 2.18 – 1.96 (m, 3 H), 1.83 - 1.72 (m, 1 H), 1.69 - 1.43 (m, 2 H)
I-276	MS *m/z* 498.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1 H), 8.83 (d, J = 5.63 Hz, 1 H), 7.67 (d, J=7.38 Hz, 1 H), 7.63 - 7.57 (m, 1 H), 7.52 -7.46 (m, 2 H), 7.19 (d, J = 5.50 Hz, 1 H), 6.68 (t, J = 76.29 Hz, 1 H), 4.53 - 4.40 (m, 1 H), 3.94 (t, J = 5.75 Hz, 2 H), 3.77 (s, 3 H), 3.23 - 3.16 (m, 1 H), 2.90 - 2.82 (m, 1 H), 2.71 - 2.61 (m, 2 H), 2.18 - 1.98 (m, 3 H), 1.83 - 1.73 (m, 1 H), 1.67 - 1.44 (m, 2 H)
I-304	MS *m/z* 368.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.08 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.79 (dd, J = 8.4, 4.4 Hz, 1H), 6.67 – 6.58 (m, 2H), 4.56 – 4.47 (m, 1H), 3.13 – 2.96 (m, 1H), 2.70 – 2.52 (m, 1H), 2.50 – 2.24 (m, 7H), 2.11 – 1.96 (m, 1H), 1.94 – 1.82 (m, 1H), 1.80 – 1.60 (m, 2H). NH and OH not observed. 1H under solvent.
I-314	MS *m/z* 359.4, 361.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.54 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.46 – 4.28 (m, 1H), 3.26 – 3.12 (m, 3H), 2.95 – 2.76 (m, 3H), 2.61 – 2.29 (m, 5H), 2.20 (p, J = 7.5 Hz, 2H), 2.11 – 1.98 (m, 1H), 1.98 – 1.85 (m, 1H), 1.85 – 1.69 (m, 1H), 1.69 – 1.47 (m, 1H). 1 OH and 1 NH signals not observed.

Example 6

Preparation of Compounds I-141 and I-142



Step 1. 1-(4-Chloro-2-(methoxymethoxy)-6-methylphenyl)-N-((R)-1-methylpiperidin-3 -yl)pyrido[3,4-d]pyridazin-4-amine

To a solution of 1-chloro-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (Intermediate 20a, 150 mg, 0.54 mmol) in DMF (2 mL) and water (0.4 ml) was added K_2CO_3 (150 mg, 1.1 mmol), XPhos Pd G4 (49 mg, 0.05 mmol) and 2-[4-chloro-2-(methoxymethoxy)-6-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 5h, 169 mg, 0.54 mmol), heat to 100 degrees under the protection of nitrogen and stirred for 1h, monitored by LCMS. After that, the mixture was concentrated and purified by silica gel column (DCM:MeOH=10:1) to give 1-(4-chloro-2-(methoxymethoxy)-6-methylphenyl)- N-((R)-1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine as yellow oil. MS *m/z* 428.1 $[M+H]^+$.

Step 2. 5-Chloro-3-methyl-2-(4-(((R)-1-methylpiperidin-3-yl) amino)pyrido[3,4-d]pyridazin-1-yl)phenol

To a solution of 1-[4-chloro-2-(methoxymethoxy)-6-methyl-phenyl] -N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (60 mg, 0.14 mmol) in DCM (2 mL) was added HCl in 1,4-dioxane (2 mL, 4 mol/L), stirred for 1h, monitored by LCMS. After that, sodium bicarbonate saturated solution was added in to adjust pH to 8. The mixture was extracted with DCM (10 mL x 3). The combined organic was dried over Na_2SO_4, concentrated to give a crude which was purified by Prep-HPLC to get 5-chloro-3-methyl-2-(4-(((R)-1-methylpiperidin-3-yl)amino)pyrido[3,4-d]pyridazin-1-yl)phenol (36 mg, 66.8% yield) as yellow solid. MS *m/z*

384.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.90 (s, 1H), 9.79 (s, 1H), 8.82 (d, *J* = 5.6 Hz, 1H), 7.60 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.96 – 6.91 (m, 1H), 6.89 – 6.84 (m, 1H), 4.52 – 4.39 (m, 1H), 3.18 – 3.08 (m, 1H), 2.80 – 2.70 (m, 1H), 2.29 – 2.20 (m, 3H), 2.11 – 1.94 (m, 3H), 1.91 (d, *J* = 6.7 Hz, 3H), 1.83 – 1.75 (m, 1H), 1.69 – 1.57 (m, 1H), 1.54 – 1.42 (m, 1H).

Step 3. 1-(2-(Methoxymethoxy)-4,6-dimethylphenyl)- N-((R)-1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine

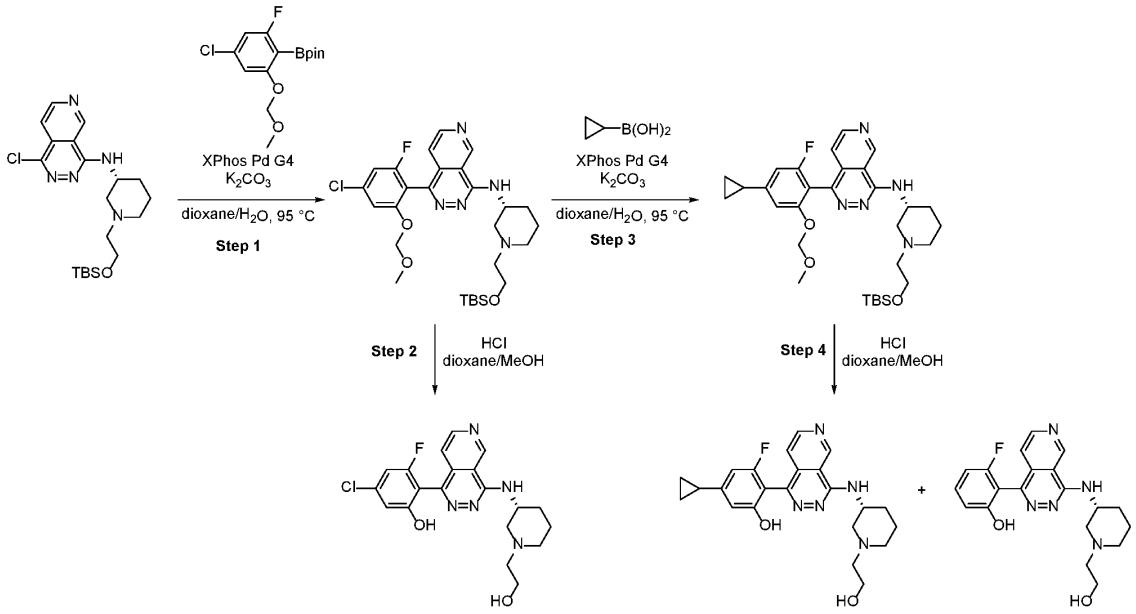
To a solution of 1-[4-chloro-2-(methoxymethoxy)-6-methyl-phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (100 mg, 0.23 mmol) in DMF (1 ml) and water (0.2 ml) was added K_2CO_3 (65 mg, 0.47 mmol), XPhos Pd G4 (22 mg, 0.023 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (44 mg, 0.35 mmol), heat to 100 degrees under nitrogen and stir for 1 hour. After that, the mixture was concentrated to dry. Purification by SGC (DCM:MeOH=10:1) provided 1-(2-(methoxymethoxy)-4,6-dimethylphenyl)-N-((R)-1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine(60 mg, 63% yield) as yellow oil. MS *m/z* 408.1 $[M+H]^+$.

Step 4. 3,5-Dimethyl-2-(4-(((R)-1-methylpiperidin-3-yl)amino)pyrido[3,4-d]pyridazin -1-yl)phenol

To a solution of 1-[2-(methoxymethoxy)-4,6-dimethyl-phenyl]-N-[(3R)-1-methyl- 3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (60 mg, 0.15 mmol) in DCM (2 mL) was added HCl in 1,4-dioxane (2 mL, 4 mol/L), and stirred for 1h. After that, sodium bicarbonate saturated solution was added to adjust pH to 8. The mixture was extracted with DCM (10 mL x 3). The combined organic was dried over Na_2SO_4, concentrated to give a crude which was purified by Prep-HPLC to get 3,5-dimethyl-2-(4-(((R)-1-methylpiperidin-3-yl)amino)pyrido[3,4-d]pyridazin-1-yl)phenol (36 mg, 67.2% Yield) as yellow solid. MS *m/z* 364.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.77 (d, *J* = 1.1 Hz, 1H), 9.22 (d, *J* = 8.7 Hz, 1H), 8.80 (d, *J* = 5.6 Hz, 1H), 7.53 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.08 (dd, *J* = 5.5 Hz, 1.1 Hz, 1H), 6.65 (s, 1H), 6.63 (d, *J* = 2.0, 1H), 4.53 – 4.37 (m, 1H), 3.20 – 3.07 (m, 1H), 2.83 – 2.72 (m, 1H), 2.28 (s, 3H), 2.26 (d, *J* = 5.3 Hz, 3H), 2.08 – 1.92 (m, 3H), 1.87 (d, *J* = 6.9 Hz, 3H), 1.82 – 1.75 (m, 1H), 1.69 – 1.57 (m, 1H), 1.54 – 1.42 (m, 1H).

Example 7

Preparation of Compounds I-282, I-284, and I-285



Step 1: 1-[4-Chloro-2-fluoro-6-(methoxymethoxy)phenyl]-*N*-[(3*R*)-1-[2-[tert-butyl-(dimethyl)silyl]oxyethyl]-3-piperidyl]pyrido[3,4-*d*]pyridazin-4-amine

1-Chloro-*N*-[(3*R*)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (Intermediate 20c, 0.150 g, 0.355 mmol), 2-[4-chloro-2-fluoro-6-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 5d, 0.197 g, 0.622 mmol), and XPhos Pd G4 (0.025 g, 0.028 mmol) were added to a vial and evacuated and refilled with Ar. The mixture was dissolved in dioxane (1.8 mL) and K_2CO_3 (2 M, 0.53 mL, 1.07 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 4 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 10%) gave an orange foam. MS *m/z* 576.6 $[M+H]^+$.

Step 2. 5-Chloro-3-fluoro-2-[4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]pyrido[3,4-d]-pyridazin-1-yl]phenol formic acid salt

To 1-[2-fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-*N*-[(3*R*)-1-[2-[tert-butyl(dimethyl)silyl]-oxyethyl]-3-piperidyl]pyrido[3,4-*d*]pyridazin-4-amine (0.070 g, 0.12 mmol) in MeOH (0.5 mL) was added HCl/dioxane (4M, 1.0 mL) and stirred for 1.5 h. The

mixture was diluted with DCM/iPrOH (9:1) and washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a tan solid (0.013 g, 23%). MS *m/z* 418.4, 420.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1 H), 8.84 (d, *J* = 5.50 Hz, 1 H), 8.17 (s, 1 H, formic acid), 7.68 (d, *J* = 7.63 Hz, 1 H), 7.22 (d, *J* = 5.63 Hz, 1 H), 7.04 (d, *J* = 9.13 Hz, 1 H), 6.91 (s, 1 H), 4.55-4.33 (m, 2 H), 3.53 (t, *J* = 6.00 Hz, 2 H), 3.18 (d, *J* = 10.3 Hz, 1 H), 2.89 – 2.79 (m, 1 H), 2.48 – 2.44 (m, 2 H), 2.19-1.95 (m, 3 H), 1.84-1.71 (m, 1 H), 1.68-1.42 (m, 2 H). 1H not observed (OH).

Step 3: 1-[4-Cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-*N*-[(3*R*)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine

1-[2-Fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-*N*-[(3*R*)-1-[2-[tert-butyl(dimethyl)silyl]-oxyethyl]-3-piperidyl]pyrido[3,4-*d*]pyridazin-4-amine (0.140 g, 0.243 mmol), cyclopropyl boronic acid (0.042 g, 0.487 mmol), and XPhos Pd G4 (0.022 g, 0.024 mmol) were added to a vial and evacuated and refilled with Ar. The mixture was dissolved in dioxane (1.2 mL) and K_2CO_3 (2 M, 0.37 mL, 0.73 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 4 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 10%) gave an tan foam, which is a mixture of the title compound and des-Cl by-product. This mixture was applied to the next step without further purification. MS *m/z* 582.7 $[M+H]^+$

Step 4: 5-Cyclopropyl-3-fluoro-2-[4-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-pyrido[3,4-d]pyridazin-1-yl]phenol formic acid salt

HCl/dioxane (4M, 1.0 mL) was added to the intermediate prepared from step 3. The reaction was stirred for 1.5 h, then diluted with DCM/iPrOH (9:1) and washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave 5-cyclopropyl-3-fluoro-2-[4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]-pyrido[3,4-*d*]pyridazin-1-yl]phenol (27 mg, 24%) and 3-fluoro-2-[4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]pyrido[3,4-*d*]pyridazin-1-yl]phenol, respectively.

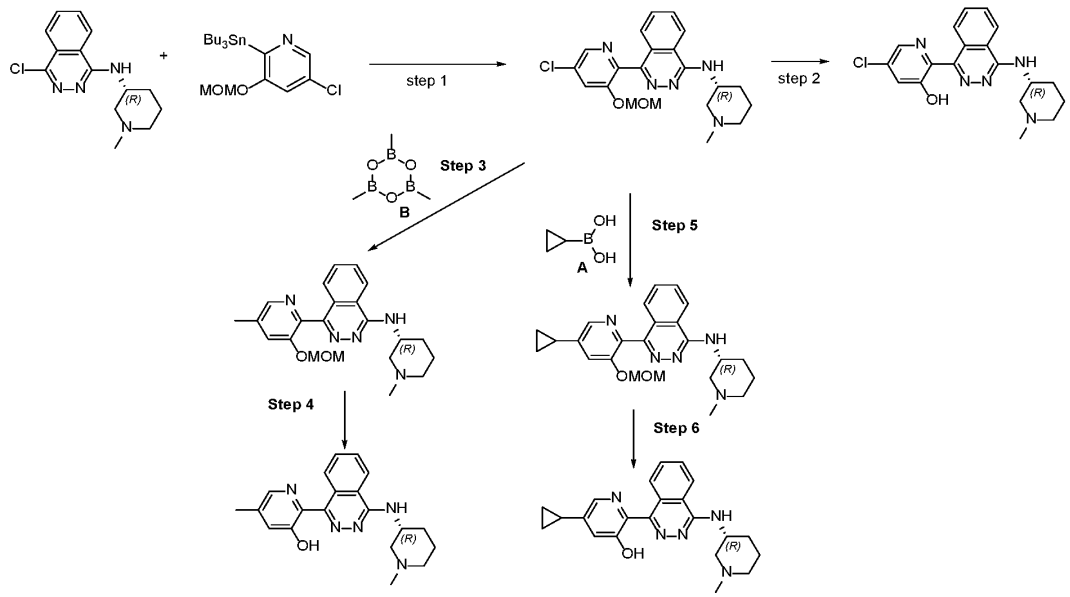
5-Cyclopropyl-3-fluoro-2-[4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]-pyrido[3,4-*d*]pyridazin-1-yl]phenol formic acid salt: MS *m/z* 424.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-

d_6) δ 9.87 (br , 1 H), 9.77 (s, 1 H), 8.83 (d, *J* = 5.63 Hz, 1 H), 8.17 (s, 1 H, formic acid), 7.60 (d, *J* = 7.38 Hz, 1 H), 7.18 (d, *J* = 5.50 Hz, 1 H), 6.58 (s, 1 H), 6.52 (d, *J* = 11.51 Hz, 1 H), 4.56 - 4.38 (m, 2 H), 3.53 (t, *J*=6.63 Hz, 2 H), 3.21 - 3.14 (m, 1 H), 2.87 - 2.79 (m, 1 H), 2.48 - 2.42 (m, 2 H), 2.16 - 1.88 (m, 4 H), 1.81 - 1.70 (m, 1 H), 1.68 - 1.45 (m, 2 H), 1.05 - 0.95 (m, 2 H), 0.77 – 0.69 (m, 2 H).

3-Fluoro-2-[4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]pyrido[3,4-*d*]pyridazin-1-yl]phenol formic acid salt: MS *m/z* 384.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 1 H), 8.85 (d, J = 5.38 Hz, 1 H), 8.21 (s, 1 H, formic acid), 7.63 (d, *J* = 7.88 Hz, 1 H), 7.42 - 7.31 (m, 1 H), 7.16 (d, *J* = 6.38 Hz, 1 H), 6.89 – 6.77 (m, 2 H), 4.54 - 4.32 (m, 2 H), 3.53 (t, *J*=6.50 Hz, 2 H), 3.21 - 3.13 (m, 1 H), 2.87 - 2.78 (m, 1 H), 2.48 - 2.42 (m, 2 H), 2.15 - 1.94 (m, 3 H), 1.83 - 1.71 (m, 1 H), 1.66 - 1.43 (m, 2 H). 1H not observed (OH).

Example 8

Preparation of Compounds I-81, I-90, and I-91



Step 1. (R)-4-(5-Chloro-3-(methoxymethoxy)pyridin-2-yl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

Argon was purged for 15 min through a stirring mixture of tributyl-[5-chloro-3-(methoxymethoxy)-2-pyridyl]stannane (prepared according to International patent application publication number WO2020231977, 1 g, 2.1 mmol), 4-chloro-N-[(3R)-1-methyl-3-

piperidyl]phthalazin-1-amine (Intermediate 19a, 298 mg, 1 mmol) and cesium fluoride (650 mg, 4.27891 mmol) in DMF (15mL). Cuprous iodide (40 mg, 0.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (250 mg, 0.21 mmol) was added in and Ar was further purged for 10 min. The reaction mixture was allowed to stir at 100 °C for 1h, monitored by LCMS. The residue was purified by column chromatography (8-10% MeOH in DCM) to afford product 4-[5-chloro-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (180 mg, 0.43 mmol, 40% Yield). MS *m/z* 414.3 $[M+H]^+$.

Step 2. (R)-5-Chloro-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)pyridin-3-ol

A solution of 4-[5-chloro-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (120 mg, 0.28 mmol) in HCl (5 ml, 4M in 1,4-Dioxane) was stirred at rt. for 3h, monitored by TLC and LCMS. After the reaction, solvent was removed and the residue was redissolved in DCM and H_2O. Aqueous solution of Na_2CO_3 was added to adjust the pH value to 8. This two-phase solution was extracted with DCM. The combined organic was dried over Na_2SO_4, and concentrated. The residue was purified by Prep-HPLC to give the product 5-chloro-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]phthalazin-1-yl]pyridin-3-ol (45 mg, 42 % Yield). MS *m/z* 370.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 – 9.95 (m, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 8.05 – 7.95 (m, 1H), 7.95 – 7.83 (m, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 6.46 (s, 1H), 4.73 – 4.61 (m, 1H), 2.90 – 2.73 (m, 1H), 2.60 – 2.44 (m, 1H), 2.35 (s, 3H), 2.21 – 2.05 (m, 2H), 1.91 – 1.77 (m, 2H), 1.68 – 1.62 (m, 2H).

Step 3. (R)-4-(3-(Methoxymethoxy)-5-methylpyridin-2-yl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

To a solution of 4-[5-chloro-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (600 mg, 1.4 mmol), was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (108 g, 14mmol), potassium carbonate (560 mg, 4 mmol) and XPhos Pd G4 (200 mg, 0.2 mmol) in DMF (10 ml) and water (1 mL). The mixture was stirred at 100 °C for 3 hours under N_2 atmosphere. After reaction, solvent was removed and the residue was purified by column chromatography (6%-8% MeOH in DCM) to afford product4-[3-(methoxymethoxy)-5-methyl-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (180 mg, 32.2% Yield). MS *m/z* 394.0 $[M+H]^+$.

Step 4. (R)-5-Methyl-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)pyridin-3-

ol

A solution of 4-[3-(methoxymethoxy)-5-methyl-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (150 mg, 0.4 mmol,) in HCl (5 mL, 4M in 1,4-dioxane) was stirred at rt. for 3 h, monitored by LCMS and TLC. After the reaction, solvent was removed. The residue was re-dissolved in H_2O and DCM, and $NaHCO_3$ was added in to adjust the pH value to 8. This mixture was extracted with DCM for 3 times. The combined organic was dried over Na_2SO_4 and concentrated to give the crude product which was purified by Prep-HPLC to afford 5-methyl-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]phthalazin-1-yl]pyridin-3-ol (50 mg, 37.5% Yield) . MS *m/z* 350.0$[M+H]^+$; ^1H NMR (CHLOROFORM-d) δ: 9.98 (d, J=8.0 Hz, 1H), 8.11 (s, 1H), 7.97 (br d, J=7.5 Hz, 1H), 7.79-7.92 (m, 2H), 7.22-7.24 (m, 1H), 6.33 (br s, 1H), 4.67 (br s, 1H), 2.78 (br s, 2H), 2.45-2.57 (m, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.14 (br d, J=10.5 Hz, 1H), 1.98-2.08 (m, 1H), 1.95 (br s, 1H), 1.77-1.88 (m, 2H), 1.62 (br d, J=3.5 Hz, 1H)

Step 5. (R)-4-(5-Cyclopropyl-3-(methoxymethoxy)pyridin-2-yl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

To a solution of cyclopropylboronic acid (500 mg, 5.8 mmol) in DMF (3 mL, 38.8 mmol) was added 4-[5-chloro-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (300 mg, 0.7 mmol), sodium carbonate (200 mg, 1.8 mmol,) and XPhos Pd G4 (30 mg, 0.03mmol). The mixture was stirred at 100 ˚C for 1h under N_2 atmosphere. After the reaction, the mixture was poured into H_2O, extracted with EA(2 x 30 mL). The organic layers were dried over Na_2SO_4, concentrated and purify via flash chromatography (CH_2Cl_2/MeOH=92:8) to give 4-[5-cyclopropyl-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (80 mg, 26.3% Yield) as a solid. MS *m/z* 420.0 $[M+H]^+$.

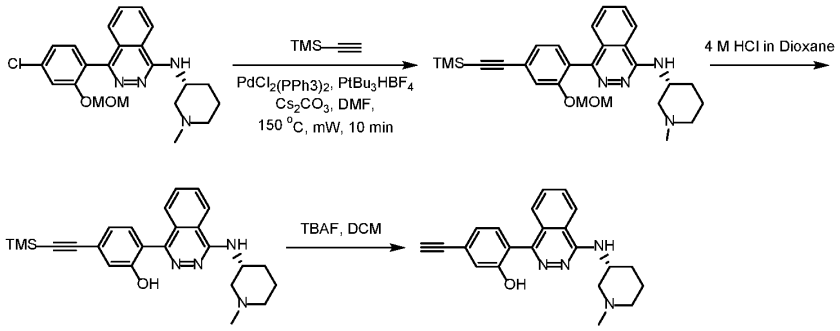
Step 6. (R)-5-Cyclopropyl-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)pyridin-3-ol

A solution of 4-[5-cyclopropyl-3-(methoxymethoxy)-2-pyridyl]-N-[(3R)-1-methyl-3-piperidyl]phthalazin-1-amine (80 mg, 0.2 mmol) in HCl (5 mL, 4M in 1,4-dioxane) was stirred at 25 ˚C for 0.5h, monitored by LCMS. After the reaction, solvent was removed. The residue was re-solved in H_2O and DCM, and $NaHCO_3$ was added in to adjust the pH value to 8. This mixture was extracted with DCM for 3 times. The combined organic was dried over Na_2SO_4 and concentrated to give the crude product which was purified by Prep-HPLC to afford 5-cyclopropyl-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]phthalazin-1-yl]pyridin-3-ol (45 mg, 62.8%

Yield) as a solid. MS *m/z* 376.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 14.65 (s, 1H), 9.80 – 9.72 (m, 1H), 8.52 – 8.42 (m, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 8.00 – 7.91 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 4.48 – 4.38 (m, 1H), 3.13 – 3.05 (m, 1H), 2.78 – 2.71 (m, 1H), 2.25 (s, 3H), 2.05 – 1.91 (m, 4H), 1.81 – 1.70 (m, 1H), 1.68 – 1.56 (m, 1H), 1.55 – 1.44 (m, 1H), 1.08 – 1.01 (m, 2H), 0.86 – 0.77 (m, 2H).

Example 9

Preparation of Compound I-226



Step 1. (*R*)-4-(2-(Methoxymethoxy)-4-((trimethylsilyl)ethynyl)phenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine

A mixture of (*R*)-5-chloro-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)phenol (prepared according to the procedure of Example 1, 41.4 mg, 0.1 mmol, 1.0 eq.), ethynyl(trimethyl)silane (86 µL, 0.6 mmol, 6.0 eq), Cs_2CO_3 (33 mg, 0.1 mmol, 1.0 eq.), $PdCl_2(PPh3)_2$ (2.1 mg, 0.003 mmol, 0.03 eq.), tri-*tert*-butylphosphonium tetrafluoroborate (1.7 mg, 0.006 mmol, 0.06 eq.), and DBU (1.5 µL, 0.01 mmol, 0.1 eq) in DMF (0.7 mL) was sparged with argon and then heated to 150 °C via microwave irradiation for 10 min. The reaction was then cooled to ambient temperature. The crude reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with brine, and the combined aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0:100 to 10:90 (10% NH_4OH in MeOH):DCM to afford (*R*)-4-(2-(methoxymethoxy)-4-((trimethylsilyl)ethynyl)phenyl)-N-(1-methylpiperidin-3-yl)phthalazin-1-amine as an impure oil. The mixture was carried forward without further purification. MS *m/z* 475.7 $[M+H]^+$.

Step 2. (*R*)-2-(4-((1-Methylpiperidin-3-yl)amino)phthalazin-1-yl)-5-((trimethylsilyl)ethynyl) phenol

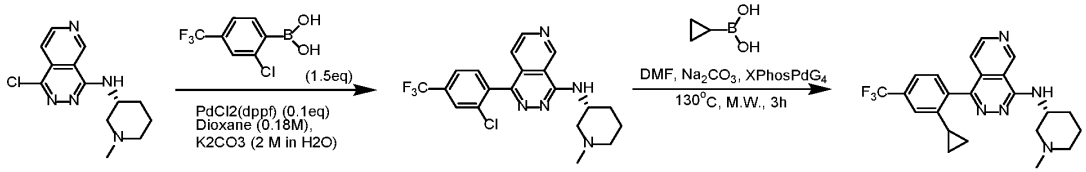
The mixture from step 1 was suspended in 4 M HCl in dioxane (2 mL) and stirred at room temperature for 4 h. Upon reaction completion solvents were removed *in vacuo.* The residue was concentrated several times from dichloromethane to remove excess HCl. The mixture was carried forward without further purification. MS *m/z* 431.6 $[M+H]^+$.

Step 3. (*R*)-5-Ethynyl-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)phenol; formic acid salt

The crude mixture from step 2 was dissolved in DCM (2 mL) and TBAF (110 µL, 2 eq, 1 M in THF) was added. The reaction was stirred at rt for 3h. Upon completion, the crude reaction mixture was diluted with sodium bicarbonate (saturated, aq.) and extracted several times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* Purification by C18 reverse phase Prep-HPLC eluting with ACN:Water with formic acid as the modifier afforded (*R*)-5-ethynyl-2-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)phenol formic acid salt (8.2 mg, 20% over 3 steps). MS *m/z* 359.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.08 (d, *J* = 1.4 Hz, 1H), 4.68 – 4.54 (m, 1H), 3.55 (s, 1H), 3.45 – 3.36 (m, 1H), 3.04 – 2.91 (m, 1H), 2.74 – 2.48 (m, 5H), 2.21 – 2.06 (m, 1H), 2.05 – 1.93 (m, 1H), 1.91 – 1.61 (m, 2H).

Example 10

Preparation of Compounds I-143 and I-194



Step 1. (R)-1-(2-Chloro-4-(trifluoromethyl)phenyl)-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine

The title compound was prepared according to the procedure of Example 1. MS *m/z* 422.2, 424.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.86 (d, J= 5.6 Hz, 1H), 8.11 (s, 1H), 7.93 (d, J= 8.0 Hz, 1H), 7.81 (d, J=7.6Hz, 1H), 7.20(d, J = 5.6 Hz, 1H), 4.50-4.48

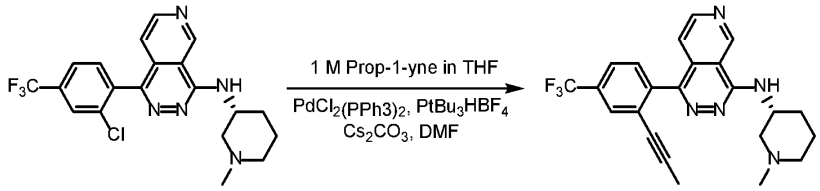
(m, 1H), 3.10(d, J=8.8 Hz, 1H), 2.73(d, J=10.8 Hz, 4H), 2.04-1.91 (m, 3H), 1.79-1.73(m, 1H), 1.66-1.56 (m, 1H), 1.52-1.43(m, 1H).

Step 2. (R)-1-(2-Cyclopropyl-4-(trifluoromethyl)phenyl)-N-(1-methylpiperidin-3-yl)pyrido[3,4-d]pyridazin-4-amine

To a mixture of 1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (100 mg, 0.237 mmol) in DMF (2 mL) were added Na_2CO_3 (64 mg, 0.604 mmol), XPhosPdG4 (8 mg, 0.009 mmol), cyclopropylboronic acid (163 mg, 1.90 mmol). The mixture was stirred for 3 h at 130 °C under microwave. After completion, the reaction mixture was cooled to room temperature and filtered. The filtrate was diluted with water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by prep-HPLC to afford title product (95 mg, 93.8% Yield) as a white solid. MS *m/z* 428.2 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 9.80 (s, 1H), 8.96 (d, *J* = 5.6 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.36 (m, 2H), 4.78 – 4.67 (m, 1H), 4.10 – 3.95 (m, 1H), 3.71 – 3.54 (m, 1H), 3.10 – 2.88 (m, 5H), 2.44 – 2.28 (m, 1H), 2.27 – 2.14 (m, 1H), 2.10 – 1.81 (m, 2H), 1.69 – 1.57 (m, 1H), 0.90 – 0.78 (m, 2H), 0.78 – 0.60 (m, 2H).

Example 11

Preparation of Compound I-228



A mixture of (*R*)-1-(2-chloro-4-(trifluoromethyl)phenyl)-*N*-(1-methylpiperidin-3-yl)pyrido[3,4-*d*]pyridazin-4-amine (Example 10, step 1, 163 mg, 0.15 mmol, 1 eq), prop-1-yne (1M in THF, 900 µL, 0.9 mmol, 6 eq), Cs_2CO_3 (33 mg, 0.1 mmol, 1 eq), $PdCl_2(PPh3)_2$ (3.2 mg, 0.0045 mmol, 0.03 eq), tri-*tert*-butylphosphonium tetrafluoroborate (2.6 mg, 0.009 mmol, 0.06 eq), and DBU (2.2 µL, 0.015 mmol, 0.1 eq) in DMF (1.1 mL) was sparged with argon and then heated to 110 °C via microwave irradiation for 3h. After the reaction was cooled to ambient temperature, the crude reaction mixture was diluted with ethyl acetate and then filtered through celite. The filtrate was washed with brine, and the combined aqueous phase was extracted with

ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0:100 to 10:90 (10%NH_4OH in MeOH):DCM followed by C18 reverse phase Prep-HPLC eluting with ACN:Water with formic acid as the modifier to afford (*R*)-*N*-(1-methylpiperidin-3-yl)-1-(2-(prop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)pyrido[3,4-*d*]pyridazin-4-amine formic acid salt (2.2 mg, 3.1%). MS *m/z* 426.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.74 (s, 1H), 8.86 (d, *J* = 5.7 Hz, 1H), 8.54 (s, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 5.8 Hz, 1H), 4.73 – 4.60 (m, 1H), 3.30 – 3.25 (m, 1H), 2.95 – 2.75 (m, 1H), 2.58 – 2.35 (m, 5H), 2.20 – 2.05 (m, 1H), 2.03 – 1.89 (m, 1H), 1.88 – 1.68 (m, 2H), 1.65 (s, 3H).

The compounds below were prepared according to the procedure of Example 11 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-13	MS *m/z* 369.1 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 10.16 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 7.84 (dd, J = 11.2, 4.1 Hz, 1H), 7.78 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.10 (d, J = 7.3 Hz, 1H), 7.02 (s, 1H), 7.02 – 7.00 (m, 1H), 4.48 – 3.36 (s, 1H), 3.15 – 3.05 (m, 1H), 2.78 – 2.71 (m, 1H), 2.26 (s, 3H), 2.10 – 1.87 (m, 3H), 1.82 – 1.73 (s, 1H), 1.70 – 1.55 (m, 1H), 1.54 – 1.40 (m, 1H).
I-32	MS *m/z* 419.3 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 8.32 (d, J = 8 Hz, 1H), 7.85-7.97 (m, 3H), 7.82 (t, J = 7 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 4.40-4.46 (m, 1H), 3.40-3.45 (m, 1H), 3.00-3.05 (m, 1H), 2.91 (s, 3H), 2.71 (t, J = 10 Hz, 2H), 2.20-2.25 (m, 1H), 1.88-1.95 (m, 1H), 1.65-1.83 (m, 2H). Three exchangeable protons are not seen.
I-37	MS *m/z* 402.7 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 8.61 (s, 1H), 8.33 (d, J = 8 Hz, 1H), 7.95 (s, 1H), 7.91 (t, J = 8 Hz, 1H), 7.84 (t, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.56-7.60 (m, 2H), 7.50 (d, J = 8 Hz, 1H), 4.59-4.64 (m, 1H), 3.05-3.12 (m, 1H), 2.70-2.80 (m, 1H), 2.30-2.50 (m, 5H), 2.05-2.15 (m, 1H), 1.88-1.97 (m, 1H), 1.50-1.85 (m, 2H). Two exchangeable protons are not seen.
I-38	MS *m/z* 433.3 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 8.32 (d, J = 8 Hz, 1H), 7.85-7.97 (m, 3H), 7.82 (t, J = 7 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 4.55-4.65 (m, 1H), 3.05-3.10 (m, 1H), 2.91 (s, 3H), 2.68-2.76 (m, 1H), 2.30-2.45 (m, 5H), 2.03-2.17 (m, 1H), 1.60-1.95 (m, 3H). Two exchangeable protons are not seen.
I-39	MS *m/z* 411.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.28 (d, J = 8.2 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.80 – 7.72 (m, 2H), 7.68 – 7.63 (m, 2H), 7.47 – 7.39 (m, 3H), 7.38 – 7.32 (m, 1H), 7.28 – 7.22 (m, 2H), 4.62 – 4.53 (m, 1H), 3.21 – 3.03 (m, 1H), 2.75 – 2.61 (m, 1H), 2.36 (s, 5H), 2.10 – 1.97 (m, 1H), 1.92 – 1.82 (m, 1H), 1.80 – 1.57 (m, 2H).
I-40	MS *m/z* 411.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 8.39 (d, J = 8.0 Hz, 1H), 7.88 – 7.82 (m, 1H), 7.82 – 7.75 (m, 1H), 7.68 – 7.61 (m, 3H),

	7.59 – 7.53 (m, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.11 – 7.05 (m, 2H), 4.51 – 4.38 (m, 1H), 3.14 – 3.06 (m, 1H), 2.76 – 2.69 (m, 1H), 2.23 (s, 3H), 2.01 – 1.88 (m, 3H), 1.80 – 1.70 (m, 1H), 1.69 – 1.55 (m, 1H), 1.54 – 1.39 (m, 1H).
I-49	MS *m/z* 375.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.91 – 7.74 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.76 – 6.71 (m, 1H), 4.77 – 4.65 (m, 1H), 2.88-2.85 (m, 2H), 2.56-2.54 (m, 1H), 2.36 (s, 3H), 2.20-2.09 (m, 3H), 1.96 – 1.84 (m, 2H), 1.67-1.64 (m, 2H), 1.34 – 1.20 (m, 1H), 1.07 – 0.95 (m, 2H), 0.87 – 0.74 (m, 2H).
I-52	MS *m/z* 417.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ： 9.78 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.92 – 7.74 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.14 (s, 1H), 7.01 – 6.91 (m, 2H), 6.33 (s, 1H), 4.45 (s, 3H), 3.81 – 3.72 (m, 2H), 2.88 (s, 1H), 2.33 (d, J = 32.0 Hz, 5H), 2.23 – 2.10 (m, 2H), 2.06 – 1.95 (m, 2H), 1.88 – 1.77 (m, 1H), 1.72 – 1.60 (m, 1H), 1.59 – 1.48 (m, 1H).
I-58	MS *m/z* 416.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4-d4) δ： 8.29 (d, J = 8.0 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.82 – 7.76 (m, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.12 – 7.06 (m, 1H), 7.02 (d, J = 4.0 Hz, 1H), 6.28 (s, 1H), 4.63 – 4.53 (m, 1H), 3.96 – 3.89 (m, 2H), 3.79 – 3.71 (m, 2H), 3.25 – 3.15 (m, 1H), 2.80 – 2.70 (m, 1H), 2.62 (s, 3H), 2.45 – 2.33 (m, 5H), 2.00 – 2.10 (s, 1H), 1.95 – 1.85 (m, 1H), 1.83 – 1.60 (m, 2H).
I-59	MS *m/z* 370.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.69 (s, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.55 (s, 1H), 7.50 (d, J = 4.0 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.04-7.03 (m, 2H), 4.71 (m, 1H), 3.64 (m, 1H), 3.23 (m, 1H), 2.92 (m, 2H), 2.76 (s, 3H), 2.15 (m, 2H), 1.91 (m, 2H).
I-60	MS *m/z* 370.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.95 (m, 2H), 8.54 (s, 1H), 8.22 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.08-7.06 (m, 2H), 4.65 (m, 1H), 3.61 (m, 1H), 3.21 (m, 1H), 2.87 (m, 2H), 2.74 (s, 3H), 2.13 (m, 2H), 1.98 – 1.69 (m, 2H).
I-70	MS *m/z* 387.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 7.86 (t, *J* = 11.2, 4.1 Hz, 1H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.02 (dd, *J* = 9.0, 1.9 Hz, 1H), 6.94 – 6.85 (m, 1H), 4.51 – 4.36 (m, 1H), 3.17 – 3.04 (m, 1H), 2.83 – 2.69 (m, 1H), 2.23 (s, 3H), 2.03 – 1.85 (m, 3H), 1.81 – 1.71 (m, 1H), 1.66 – 1.56 (m, 1H), 1.54 – 1.41 (m, 1H).
I-76	MS *m/z* 370.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 9.63 (d, J = 0.8 Hz, 1H), 8.79 (d, J = 5.6 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.31 (dd, J = 7.6, 1.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 4.66 – 4.54 (m, 1H), 3.24 – 3.04 (m, 1H), 2.85 – 2.64 (m, 1H), 2.52 – 2.26 (m, 5H), 2.12 – 1.97 (m, 1H), 1.96 – 1.83 (m, 1H), 1.82 – 1.55 (m, 2H).
I-77	MS *m/z* 376.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 9.71 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 7.61 (dd, J = 5.6, 0.8 Hz, 1H), 7.23 (dd, J = 7.6, 1.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 7.02 – 6.96 (m, 1H), 4.70 – 4.58 (m, 1H), 3.31 – 3.19 (m, 1H), 2.94 – 2.81 (m, 1H), 2.58 – 2.39 (m, 5H), 2.19 – 2.07 (m, 2H), 2.00 – 1.90 (m, 1H), 1.88 – 1.65 (m, 3H), 1.03 – 0.93 (m, 2H), 0.74 – 0.68 (m, 2H).
I-89	MS *m/z* 376.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 8.94 (d, *J* = 5.7 Hz, 1H), 8.03 (d, *J* = 5.7 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* =

	1.9 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.79 – 4.64 (m, 1H), 2.92 – 2.74 (m, 2H), 2.58 – 2.45 (m, 1H), 2.35 (s, 3H), 2.18 – 2.05 (m, 2H), 1.97 – 1.78 (m, 2H), 1.73 – 1.56 (m, 2H), 1.07 – 0.98 (m, 2H), 0.83 – 0.74 (m, 2H).
I-93	MS *m/z* 404.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD-d4) δ 8.25 (d, J = 8.0 Hz, 1H), 7.96 – 7.73 (m, 3H), 7.22 (d, J = 8.4 Hz, 1H), 6.27 (dd, J = 8.4, 2.0 Hz, 1H), 6.19 (d, J = 2.0 Hz, 1H), 4.57 – 4.46 (m, 1H), 3.37 – 3.31 (m, 4H), 3.18 – 3.02 (m, 1H), 2.75 – 2.60 (m, 1H), 2.36 (s, 5H), 2.14 – 1.94 (m, 5H), 1.91 – 1.82 (m, 1H), 1.81 – 1.71 (m, 1H), 1.69 – 1.55 (m, 1H).
I-107	MS *m/z* 418.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ: 8.37 (d, J = 8.0 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.81 – 7.74 (m, 1H), 7.51 (d, J = 4.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 6.93 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 4.50 – 4.404 (m, 1H), 3.45 – 3.34 (m, 1H), 3.18 – 3.07 (m, 2H), 2.94 – 2.83 (m, 2H), 2.83 – 2.76 (m, 1H), 2.77 – 2.69 (m, 1H), 2.48 (s, 3H), 2.29 (s, 3H), 2.14 – 1.93 (m, 4H), 1.93 – 1.86 (m, 1H), 1.83 – 1.74 (m, 1H), 1.70 – 1.58 (m, 1H), 1.55 – 1.44 (m, 1H).
I-130	MS *m/z* 412.8 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 9.78-9.82 (m, 1H), 8.92 (d, J=5.6 Hz, 1H), 8.38 (s, 1H), 8.20 (d, J=8.5 Hz, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.49-7.54 (m, 1H), 4.69 (dt, J=8.5, 4.5 Hz, 1H), 3.08-3.25 (m, 1H), 2.75 (br s, 1H), 2.32-2.49 (m, 5H), 2.11 (br s, 1H), 1.87-1.97 (m, 1H), 1.68-1.86 (m, 2H).
I-132	MS *m/z* 420.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H),8.86 (d, J= 5.6 Hz, 1H), 7.72 (d, J= 7.6 Hz, 1H),7.60-7.57 (m, 1H), 7.53 (s, 1H),7.53-7.52 (m, 1H), 7.26 (s, 1H),7.25 (t, J= 81.2 Hz, 1H),4.47-4.43 (m, 1H), 3.09 (d, J= 8.0 Hz, 1H),2.72 (d, J= 10.8 Hz, 1H),2.22 (s, 3H),2.03-1.89 (m, 3H), 1.79-1.75 (m, 1H), 1.66-1.57 (m, 1H), 1.51-1.42 (m, 1H).
I-133	MS *m/z* 419.1, 421.1 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 8.40 (s, 1H, formic acid), 8.35 (d, J = 9.0 Hz, 1H), 7.95 (t, J = 7.7 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.56 – 7.46 (m, 4H), 6.83 (td, J = 73.5, 13.4 Hz, 1H), 4.72 – 4.63 (m, 1H), 3.91 – 3.66 (m, 1H), 3.51 – 3.38 (m, 1H), 3.13 – 2.96 (m, 2H), 2.89 (s, 3H), 2.34 – 2.12 (m, 2H), 2.03 – 1.81 (m, 2H); 1H not observed (NH)
I-134	MS *m/z* 400.2 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 9.72 (s, 1H), 8.89 (d, J = 5.6 Hz, 1H), 8.36 (s, 1H, formic acid), 7.42 (d, J = 7.0 Hz, 2H), 7.29 (d, J = 7.8 Hz, 1H), 7.24 (s, 1H), 6.78 (td, J = 74.2, 8.2 Hz, 1H), 4.76 – 4.69 (m, 1H), 3.92 – 3.77 (m, 1H), 3.50 – 3.37 (m, 1H), 3.15 – 2.96 (m, 2H), 2.90 (s, 3H), 2.51 (s, 3H), 2.33 – 2.14 (m, 2H), 2.03 – 1.84 (m, 2H); 1H not observed (NH)
I-135	MS *m/z* 399.2 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 8.34 – 8.31 (m, 2H, including formic acid), 7.94 (t, J = 7.7 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.22 (s, 1H), 6.74 (td, J = 74.8, 13.9 Hz, 1H), 4.71 – 4.63 (m, 1H), 3.96 – 3.72 (m, 1H), 3.56 – 3.39 (m, 1H), 3.16 – 2.94 (m, 2H), 2.91 (s, 3H), 2.50 (s, 3H), 2.30 – 2.14 (m, 2H), 2.03 – 1.83 (m, 2H); 1H not observed (NH)
I-136	MS *m/z* 359.3 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.65 (s, 1H), 8.80 (d, J=5.6 Hz, 1H), 7.69 (s, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.38 (d, J=5.8 Hz, 1H), 4.61-4.71 (m, 1H), 3.60-3.82 (m, 1H), 3.23-3.38 (m, 1H), 2.93-3.10 (m, 2H), 2.79 (s, 3H), 2.40 (s, 3H), 1.98-2.22 (m, 2H), 1.77-1.94 (m, 2H)

I-137	MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 9.72 (s, 1H), 8.87 (d, J = 5.5 Hz, 1H), 7.97 (s, 2H), 7.75-7.80 (m, 2H), 7.55-7.63 (m, 2H), 4.60-4.70 (m, 1H), 3.15-3.25 (m, 1H), 2.70-2.80 (m, 1H), 2.28-2.48 (m, 5H), 2.05-2.15 (m, 1H), 1.90-1.98 (m, 1H), 1.60-1.85 (m, 2H). Two exchangeable protons are not seen.
I-145	MS *m/z* 456.0 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.77 (br d, J=2.6 Hz, 1H), 8.97 (d, J=5.6 Hz, 1H), 8.89 (d, J=5.6 Hz, 1H), 7.78 (d, J=5.8 Hz, 1H), 7.67 (d, J=8.5 Hz, 1H), 7.30 (d, J=5.6 Hz, 1H), 5.70 (br s, 1H), 4.68-4.83 (m, 1H), 4.37-4.61 (m, 2H), 3.78 (br s, 1H), 3.34-3.56 (m, 2H), 2.96-3.13 (m, 2H), 2.88 (s, 3H), 2.15-2.32 (m, 2H), 1.85-2.09 (m, 2H)
I-157	MS *m/z* 378.9 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.80 (s, 1H), 8.97 (d, J=5.8 Hz, 1H), 8.11 (d, J=2.1 Hz, 1H), 7.90-7.99 (m, 1H), 7.76 (d, J=8.4 Hz, 1H), 7.56 (dd, J=5.8, 0.8 Hz, 1H), 4.73-4.85 (m, 1H), 3.71-3.88 (m, 1H), 3.35-3.45 (m, 1H), 2.99-3.19 (m, 2H), 2.90 (s, 3H), 2.16-2.32 (m, 2H), 1.91-2.05 (m, 2H)
I-158	MS *m/z* 428.7 $[M+H]^+$; ^1H NMR ($DMSO-d_6$) δ: 9.74 (s, 1H), 8.76 (br d, J=5.3 Hz, 1H), 7.57-7.63 (m, 2H), 7.41 (br d, J=7.3 Hz, 1H), 7.35 (br d, J=5.0 Hz, 1H), 6.99 (br d, J=5.0 Hz, 1H), 4.33-4.47 (m, 1H), 2.95-3.13 (m, 1H), 2.63-2.70 (m, 1H), 2.04-2.22 (m, 4H), 1.80-2.00 (m, 3H), 1.64-1.78 (m, 1H), 1.48-1.62 (m, 1H), 1.41 (br dd, J=11.8, 0.8 Hz, 1H), 1.03 (br d, J=7.3 Hz, 2H), 0.69-0.91 (m, 2H)
I-170	MS *m/z* 388.2, 390.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.62 (s, 1H), 9.80 (s, 1H), 8.51(d, J = 5.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.03 (dd, J = 9.2 Hz, 2.0 Hz, 1H), 6.90 (s, 1H), 4.49-4.43 (m, 1H), 3.10 (d, J = 4.0 Hz, 1H), 2.73 (d, J = 10.4 Hz, 1H), 2.23 (s, 3H), 2.03-1.94 (m, 3H), 1.79-1.76 (m, 1H), 1.66-1.57 (m, 1H), 1.52-1.45 (m, 1H).
I-172	MS *m/z* 371.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 14.43 (s, 1H), 9.87 (s, 1H), 9.22(d, J = 5.6 Hz, 1H), 9.03 (d, J = 5.6 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 4.47-4.45 (m, 1H), 3.08 (d, J = 8.8 Hz, 1H), 2.73 (d, J = 11.6 Hz, 1H), 2.23 (s, 3H), 2.03-1.91 (m, 3H), 1.81-1.76 (m, 1H), 1.64-1.61 (m, 1H), 1.54-1.47 (m, 1H).
I-173	MS *m/z* 447.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.74 (s, 1H), 8.87 (d, J = 5.6 Hz, 1H), 8.08 (s, 1H), 8.06 - 8.01 (m, 1H), 7.89 (dd, J = 1.4, 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 5.8 Hz, 1H), 7.39 (s, 1H), 5.25 - 5.12 (m, 2H), 4.71 - 4.62 (m, 1H), 3.31 (s, 3H), 2.96 - 2.81 (m, 1H), 2.57 - 2.42 (m, 6H), 2.24 - 2.06 (m, 1H), 2.03 - 1.92 (m, 1H), 1.89 - 1.68 (m, 2H); NH wasn't observed
I-176	MS *m/z* 402.9 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.71 (s, 1H), 8.87 (d, J = 5.8 Hz, 1H), 8.05 (s, 1H), 7.73 - 7.66 (m, 2H), 7.59 - 7.52 (m, 2H), 7.36 (s, 1H), 4.75 - 4.57 (m, 1H), 2.96 - 2.82 (m, 1H), 2.61 - 2.42 (m, 6H), 2.14 (br s, 1H), 2.04 - 1.93 (m, 1H), 1.90 - 1.67 (m, 2H); OH and NH wasn't observed
I-179	MS *m/z* 368.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 1H), 9.79 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 5.6 Hz, 1H), 6.67-6.64 (m , 2H), 4.46-4.42 (m, 1H), 3.11 (d, J = 7.6 Hz, 1H), 2.73 (d, J = 10.8 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 2.03-1.95 (m , 3H), 1.79-1.76 (m , 1H), 1.66-1.57 (m, 1H), 1.52-1.45 (m, 1H).
I-188	MS *m/z* 460.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.77 - 9.73 (m, 1H), 8.88 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.59 - 7.49 (m, 1H),

	7.49 - 7.40 (m, 1H), 7.06 (s, 1H), 5.47 - 5.40 (m, 1H), 4.98 - 4.89 (m, 2H), 4.75 - 4.60 (m, 1H), 4.46 (br s, 1H), 4.40 - 4.27 (m, 1H), 3.30 - 3.19 (m, 1H), 2.88 - 2.77 (m, 1H), 2.46 (s, 5H), 2.20 - 2.06 (m, 1H), 2.00-1.94 (m, 1H), 1.89 - 1.67 (m, 2H); NH wasn't observed
I-189	MS *m/z* 468.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.7(s, 1H), 8.8(d,J=5.6 Hz 1H), 8.0(s, 1H), 7.8(d, J=8 Hz, 1H), 7.7(d,J=8Hz,1H), 7.6(s, 1H), 7.6(s, 1H), 7.2(d,J=5.6 Hz,1H),7.0(d, J=13.6 Hz ,1H), 4.7(m, 1H), 4.0(d,J=5.6 Hz,1H),3.7(d, J=5.2 Hz ,3H),3.6(m, 1H), 3.0(m, 1H), 2.98(d,J=6.8 Hz,1H), 2.91 (d,J=3.6 Hz,1H), 2.3 (dd,J=52.4Hz,2H), 2.0-1.8(m, 2H).
I-193	MS *m/z* 454.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.86 (d, J= 5.6 Hz, 1H), 8.11 (s, 1H), 7.93 (d, J= 8.0 Hz, 1H), 7.81 (d, J=7.6Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 4.50-4.48 (m, 1H), 3.10 (d, J=8.8 Hz, 1H), 2.73 (d, J=10.8 Hz, 1H),2.23 (s, 3H),2.04-1.91 (m, 3H), 1.79-1.76(m, 1H), 1.63-1.60 (m, 1H), 1.49-1.47(m, 1H).
I-195	MS *m/z* 351.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 13.87 (s, 1H), 9.86 (s, 1H), 9.43(d, J = 5.6 Hz, 1H), 9.03 (d, J = 5.6 Hz, 1H), 8.15 (d, J=1.2 Hz,1H), 7.96 (d, J = 7.2 Hz, 1H), 7.28 (d, J = 1.2 Hz, 1H), 4.46-4.45(m, 1H),3.11-3.07 (m, 1H), 2.76-2.73 (m, 1H), 2.35 (s, 3H), 2.24 (s, 3H), 2.04-1.93 (m, 3H), 1.80-1.76 (m, 1H), 1.64-1.61 (m, 1H), 1.51-1.47 (m, 1H).
I-196	MS *m/z* 394.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.89 (br s, 1H), 9.79 (s, 1H), 8.84 (d, J = 5.2 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 5.2 Hz, 1H), 6.58 (s , 1H), 6.53 (d, J = 10.8 Hz, 1H), 4.46-4.45 (m, 1H), 3.11 (d, J = 8.0 Hz, 1H), 2.73 (d, J = 10.4 Hz, 1H), 2.23 (s, 3H), 2.03-1.95 (m , 4H), 1.79-1.76 (m , 1H), 1.63-1.60 (m, 1H), 1.51-1.42 (m, 1H), 1.01 (d, J = 6.4 Hz, 2H), 0.73 (d, J = 4.0 Hz, 2H).
I-200	MS *m/z* 414.7 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.60 (s, 1H), 8.81 - 8.72 (m, 3H), 8.05 - 7.91 (m, 2H), 7.50 - 7.45 (m, 1H), 7.45 - 7.39 (m, 1H), 7.29 (t, J = 4.9 Hz, 1H), 4.63 - 4.44 (m, 1H), 3.11 - 2.96 (m, 1H), 2.60 (br s, 1H), 2.29 - 2.19 (m, 5H), 1.99 (br s, 1H), 1.79 (br dd, J = 4.1, 9.2 Hz, 1H), 1.72 - 1.50 (m, 2H); NH and OH wasn't observed
I-201	MS *m/z* 432.0 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.23 (d, J = 8.3 Hz, 1H), 7.97 (dt, J = 1.1, 7.7 Hz, 1H), 7.85 (dt, J = 1.0, 7.7 Hz, 1H), 7.63 - 7.54 (m, 2H), 7.52 - 7.44 (m, 2H), 4.08 (br t, J = 12.1 Hz, 2H), 3.80 (s, 3H), 3.23 - 3.05 (m, 2H), 2.60 - 2.50 (m, 1H), 2.43 (s, 6H), 2.14 (br d, J = 12.3 Hz, 2H), 2.00 - 1.81 (m, 2H)
I-202	MS *m/z* 464.3 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.58 (s, 1H), 8.60 (d, J=5.6 Hz, 1H), 7.78-7.91 (m, 3H), 7.08-7.20 (m, 6H), 4.56-4.67 (m, 1H), 3.37 (s, 1H), 3.04-3.24 (m, 1H), 2.72 (s, 1H), 2.37 (d, J=6.5 Hz, 3H), 2.26-2.33 (m, 1H), 2.08 (br dd, J=12.0, 7.6 Hz, 1H), 1.85-1.95 (m, 1H), 1.77 (td, J=6.6, 2.8 Hz, 1H), 1.66 (br s, 1H)
I-205	MS *m/z* 362.6 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.79 (s, 1H), 8.89 (d, J=5.6 Hz, 1H), 7.22 (d, J=5.5 Hz, 1H), 7.09 (s, 2H), 4.78-4.86 (m, 1H), 3.74-4.04 (m, 1H), 3.37-3.50 (m, 1H), 3.07-3.21 (m, 2H), 2.90-2.94 (m, 3H), 2.40 (s, 3H), 2.15-2.31 (m, 4H), 1.93 (d, J=3.1 Hz, 6H)
I-207	MS *m/z* 404.7 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.77 (s, 1H), 8.84 (d, J=5.6 Hz, 1H), 7.41 (s, 1H), 7.29 (d, J=5.5 Hz, 1H), 7.22-7.26 (m, 1H), 7.18 (dd, J=7.8,

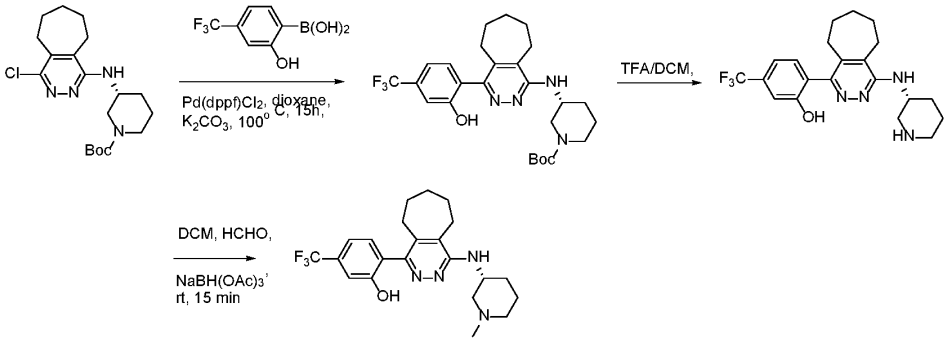
	1.9 Hz, 1H), 4.62-4.73 (m, 1H), 3.29 (br s, 1H), 3.02 (dt, J=13.8, 6.9 Hz, 1H), 2.87 (br d, J=8.0 Hz, 1H), 2.55-2.67 (m, 1H), 2.48 (s, 4H), 2.07-2.18 (m, 1H), 1.89-2.02 (m, 1H), 1.70-1.89 (m, 2H), 1.33 (d, J=6.9 Hz, 6H), 1.17 (br d, J=6.8 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H)
I-208	MS *m/z* 408.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD)) δ 9.73 (d, J = 1.0 Hz, 1H), 8.86 (d, J = 5.7 Hz, 1H), 7.31 (d, J = 5.7 Hz, 1H), 7.12 (dd, J = 8.8, 6.4 Hz, 1H), 7.02 (t, J = 8.7 Hz, 1H), 4.72 – 4.59 (m, 1H), 3.56 (s, 3H), 3.36 – 3.32 (m, 2H, 3.00 – 2.72 (m, 1H), 2.63 – 2.35 (m, 5H), 2.28 – 2.06 (m, 2H), 2.05 – 1.90 (m, 1H), 1.88 – 1.61 (m, 2H), 1.13 – 0.96 (m, 2H), 0.91 – 0.77 (m, 1H), 0.77 – 0.64 (m, 1H).
I-209	MS *m/z* 388.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.63 (s, 1H), 8.81 (s, 1H), 8.52 (s, 1H), 7.51 (ddd, J = 9.1, 6.1, 1.4 Hz, 1H), 7.36 (d, J = 5.6 Hz, 1H), 6.83 – 6.71 (m, 1H), 4.76 – 4.65 (m, 1H), 3.52 – 3.36 (m, 1H), 3.08 – 2.94 (m, 1H), 2.91 – 2.65 (m, 2H), 2.62 (s, 3H), 2.22 – 1.99 (m, 2H), 1.94 – 1.72 (m, 2H).
I-210	MS *m/z* 394.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.72 (s, 1H), 8.87 (dd, J = 5.7, 2.1 Hz, 1H), 8.54 (s, 1H), 7.44 – 7.39 (m, 1H), 7.36 – 7.30 (m, 1H), 6.76 (dd, J = 10.0, 8.2 Hz, 1H), 5.06 – 4.93 (m, 1H), 4.71 – 4.61 (m, 1H), 3.53 – 3.35 (m, 1H), 2.95 – 2.79 (m, 2H), 2.57 – 2.38 (m, 5H), 2.22 – 2.05 (m, 1H), 2.02 – 1.90 (m, 1H), 1.88 – 1.64 (m, 2H), 1.43 – 1.31 (m, 3H).
I-211	MS *m/z* 388.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.02 (dd, J = 4.3, 1.5 Hz, 1H), 8.73 (d, J = 8.5 Hz, 1H), 8.53 (s, 1H), 7.82 (dd, J = 8.4, 4.4 Hz, 1H), 7.46 (dd, J = 8.9, 6.0 Hz, 1H), 6.75 (t, J = 8.7 Hz, 1H), 4.69 – 4.58 (m, 1H), 3.43 – 3.32 (m, 1H), 3.03 – 2.88 (m, 1H), 2.77 – 2.44 (m, 5H), 2.21 – 2.06 (m, 1H), 2.04 – 1.93 (m, 1H), 1.91 – 1.65 (m, 2H).
I-216	MS *m/z* 348.5 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.75 (s, 1H), 8.84 (d, J=5.6 Hz, 1H), 7.30 (d, J=5.6 Hz, 1H), 7.24 (s, 1H), 7.19 (s, 2H), 4.62-4.73 (m, 1H), 3.22-3.45 (m, 2H), 2.81-2.97 (m, 1H), 2.43-2.55 (m, 5H), 2.42 (s, 3H), 2.08-2.15 (m, 1H), 2.07 (s, 3H), 1.97 (br dd, J=9.2, 4.6 Hz, 1H), 1.71-1.90 (m, 2H)
I-217	MS *m/z* 359.5 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.78 (s, 1H), 8.92 (d, J=5.8 Hz, 1H), 8.37 (s, 1H), 7.86 (s, 1H), 7.79 (d, J=7.5 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.32 (dd, J=5.7, 0.7 Hz, 1H), 4.71-4.80 (m, 1H), 3.71-3.93 (m, 1H), 3.42 (br d, J=12.1 Hz, 1H), 2.96-3.13 (m, 2H), 2.90 (s, 3H), 2.20-2.29 (m, 2H), 2.19 (s, 3H), 1.88-2.06 (m, 2H)
I-218	MS *m/z* 382.5 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.80 (s, 1H), 8.91 (d, J=5.6 Hz, 1H), 8.40 (s, 2H), 7.31 (s, 2H), 7.22 (dd, J=5.6, 0.8 Hz, 1H), 4.71-4.87 (m, 1H), 3.76-4.00 (m, 1H), 3.35-3.52 (m, 1H), 3.07-3.20 (m, 2H), 2.93 (s, 3H), 2.14-2.34 (m, 2H), 1.89-2.05 (m, 8H)
I-225	MS *m/z* 399.6 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 8.29 (d, J = 8.2 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.00 (dd, J = 7.8, 1.5 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 4.67 – 4.57 (m, 1H), 3.69 – 3.51 (m, 1H), 3.22 – 3.09 (m, 1H), 2.92 – 2.73 (m, 2H), 2.70 (s, 3H), 2.26 – 2.13 (m, 1H), 2.12 – 2.01 (m, 1H), 1.98 – 1.70 (m, 2H), 1.57 – 1.44 (m, 1H), 0.98 – 0.86 (m, 2H), 0.84 – 0.71 (m, 2H).
I-227	MS *m/z* 373.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.98 (s, 1H), 4.68 – 4.54

	(m, 1H), 3.59 – 3.41 (m, 1H), 3.14 – 2.97 (m, 1H), 2.82 – 2.64 (m, 2H), 2.62 (s, 3H), 2.20 – 2.09 (m, 1H), 2.09 – 1.98 (m, 4H), 1.92 – 1.70 (m, 2H).
I-232	MS *m/z* 468.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.74 (s, 1 H), 8.79 (d, J =5.6 Hz 1 H), 8.23 (s, 1 H), 7.90 (d, J =7.6 Hz, 1 H), 7.77 (d, J =8.0 Hz, 1 H), 7.33 (d, J =2.4 Hz, 1 H), 7.22 (d, J =5.6 Hz, 1 H), 5.97 (d, J=8.8 Hz, 1 H), 4.77-4.75 (m, 1 H), 4.05-4.03 (m,1 H), 3.64 (s ,3 H), 3.64-3.60 (m, 1 H), 3.00 (d, J =5.2 Hz, 3 H), 3.10-2.95 (m ,2 H), 2.39-2.36 (m, 1 H), 2.24-2.21 (m, 1 H), 2.06-1.88 (m, 2 H)
I-240	MS *m/z* 465.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H), 8.68 (d, J= 5.6 Hz, 1H), 8.33 –8.27 (m, 2H), 8.02 –7.96 (m, 2H), 7.83 (d, J= 7.9 Hz, 1H), 7.68 (d, J= 7.4 Hz, 1H), 7.60 (d, J= 7.8 Hz, 1H), 7.21 (dd, J= 7.8, 4.9 Hz, 1H), 7.11 (d, J= 5.5 Hz, 1H), 4.44 (s, 1H), 3.10 (s, 1H), 2.75 (d, J= 10.5 Hz, 1H), 2.25 (s, 3H), 1.97 (s, 3H), 1.75 (s, 1H), 1.61 (d, J= 12.0 Hz, 1H), 1.44 (s, 1H).
I-241	MS *m/z* 409.5, 411.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.50 – 7.39 (m, 3H), 7.28 (t, J = 73.7 Hz, 1H), 6.08 (d, J = 7.9 Hz, 1H), 4.32 – 4.18 (m, 1H), 3.00 – 2.91 (m, 1H), 2.74 (t, J = 7.8 Hz, 2H), 2.67 (t, J = 8.0 Hz, 2H), 2.18 (s, 3H), 2.04 – 1.94 (m, 3H), 1.94 – 1.81 (m, 3H), 1.75 – 1.65 (m, 1H), 1.62 – 1.48 (m, 1H), 1.43 – 1.30 (m, 1H)
I-244	MS *m/z* 389.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.53 (s, 1H, formic acid), 7.34 – 7.28 (m, 1H), 7.22 – 7.15 (m, 1H), 7.11 (s, 1H), 6.73 (t, J = 75.04, 1H), 4.50 – 4.40 (m, 1H), 3.50 – 3.39 (m, 1 H), 3.13 – 3.00 (m, 1 H), 2.87 (t, J =7.63 Hz, 2H), 2.79 (t, J = 8.25 Hz, 2 H), 2.72 – 2.54 (m, 5H), 2.43 (s, 3H), 2.20 – 1.92 (m, 4H), 1.91 – 1.75 (m, 1H), 1.75 – 1.58 (m, 1H). 1H not observed (NH)
I-246	MS *m/z* 415.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.30 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.99 (s, 1H), 6.75 (t, J = 74.04 Hz, 1H), 4.57 – 4.45 (m, 1H), 3.79 – 3.58 (m, 1H), 3.43 – 3.34 (m, 1H), 3.10 – 2.92 (m, 2H), 2.92 – 2.84 (m, 5H), 2.80 (t, J = 7.6 Hz, 2H), 2.20 – 2.08 (m, 4H), 2.06 – 1.97 (m, 1H), 1.97 – 1.84 (m, 1H), 1.84 – 1.68 (m, 1H), 1.12 – 1.03 (m, 2H), 0.78 (br s, 2H); 1H missing (NH)
I-247	MS *m/z* 425.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1 H), 8.84 (d, J = 5.63 Hz, 1 H), 8.19 (br s, 1 H, formic acid), 7.67 (d, J = 7.38 Hz, 1 H), 7.38 (d, J = 7.88 Hz, 1 H), 7.22 (d, J = 5.63 Hz, 1 H), 7.16 (t, J = 74.04 Hz, 1 H), 7.12 (d, J = 8.25 Hz, 1 H), 7.08 (s, 1 H), 4.53 - 4.38 (m, 1 H), 3.17 - 3.07 (m, 1 H), 2.75 (d, J=10.76 Hz, 1 H), 2.25 (s, 3 H), 2.12 – 1.93 (m, 4 H), 1.85 - 1.73 (m, 1 H), 1.68 – 1.55 (m, 1 H), 1.53 – 1.41 (m, 1 H), 1.10 – 1.02 (m, 2 H), 0.86 – 0.79 (m, 2 H)
I-248	MS *m/z* 409.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.81 (s, 1 H), 8.85 (d, J = 5.63 Hz, 1 H), 8.21 (br s, 1 H, formic acid), 7.71 (d, J = 7.50 Hz, 1 H), 7.54 (s, 1 H), 7.39 – 7.32 (m , 2 H), 7.22 (d, J = 5.63 Hz, 1 H), 6.84 (t, J = 54.66 Hz, 1 H), 4.57 - 4.40 (m, 1 H), 3.18 - 3.08 (m, 1 H), 2.76 (d, J = 11.38 Hz, 1 H), 2.25 (s, 3 H), 2.19 - 2.08 (m, 1 H), 2.07 – 1.93 (m, 3 H), 1.85 - 1.74 (m, 1 H), 1.70 - 1.55 (m, 1 H), 1.54 - 1.40 (m, 1 H), 1.13 - 1.03 (m, 2 H), 0.86 - 0.78 (m, 2 H)

I-289	MS *m/z* 422.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1 H), 8.85 (d, J=5.4 Hz, 1 H), 8.29 – 8.12 (br, 1H), 8.06 (s, 1 H, formic acid), 7.94 (d, J=8.3 Hz, 1 H), 7.79 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 4.45 - 4.58 (m, 1 H), 3.07 - 3.23 (m, 1 H), 2.80 (m, 1 H), 2.29 (s, 3 H), 1.98 - 2.22 (m, 3 H), 1.88 – 1.75 (m, 1H), 1.64 (m, 1H), 1.51 (m, 1H).
I-298	MS *m/z* 402.5 $[M+H]^+$; ^1H NMR (DMSO-d_6) δ: 9.97 – 9.69 (m, 1H), 9.05 – 8.68 (m, 1H), 7.88 – 7.77 (m, 1H), 7.74 – 7.57 (m, 2H), 7.45 (s, 1H), 7.16 – 6.93 (m, 1H), 4.66 – 4.35 (m, 1H), 3.12 (d, J = 1.3 Hz, 2H), 2.76 (dd, J = 2.6, 1.3 Hz, 1H), 2.72 – 2.67 (m, 1H), 2.51 (s, 1H), 2.26 (s, 3H), 1.99 (d, J = 18.0 Hz, 3H), 1.78 (d, J = 2.6 Hz, 1H), 1.72 – 1.57 (m, 1H), 1.50 (s, 1H).
I-307	MS *m/z* 364.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.76 (s, 1H), 9.63 (br s, 1H), 8.84 (s, 1H), 8.18 (s, 1H, formic acid), 7.54 (d, J = 7.3 Hz, 1H), 7.31 (d J = 5.88 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.86 – 6.79 (m, 2H), 4.52 – 4.39 (m, 1H), 3.16 – 3.07 (m, 1H), 2.81 – 2.70 (m, 1H), 2.63 (q, J = 7.5 Hz, 2H), 2.30 – 2.20 (m, 3H), 2.07 – 1.91 (m, 3H), 1.83 – 1.72 (m, 1H), 1.70 – 1.55 (m, 1H), 1.54 – 1.39 (m, 1H), 1.23 (t, J = 7.6 Hz, 3H)

Example 12

Preparation of Compounds I-31 and I-36



Step 1: tert-Butyl (R)-3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate

tert-Butyl (R)-3-((4-chloro-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate (Intermediate 22, 100 mg, 0.24 mmol), (2-hydroxy-4-trifluoromethyl)phenyl)boronic acid (63 mg, 0.3 mmol), Pd(dppf)Cl_2-Dichloromethane complex (20 mg, 0.024 mmol), 2M aqueous K_2CO_3 (0.3 mL, 0.6 mmol), and dioxane (0.8 mL) were heated at 100° C for 15 hours. This was then partitioned between H_2O and DCM. The organic layer was dried over $MgSO_4$ and filtered. Solvent was removed under vacuum. Purification by silica gel chromatography (0-100% EtOAc in DCM) yielded tert-butyl (R)-3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-

carboxylate (108 mg, 90%).

Step 2. (R)-2-(4-(Piperidin-3-ylamino)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol

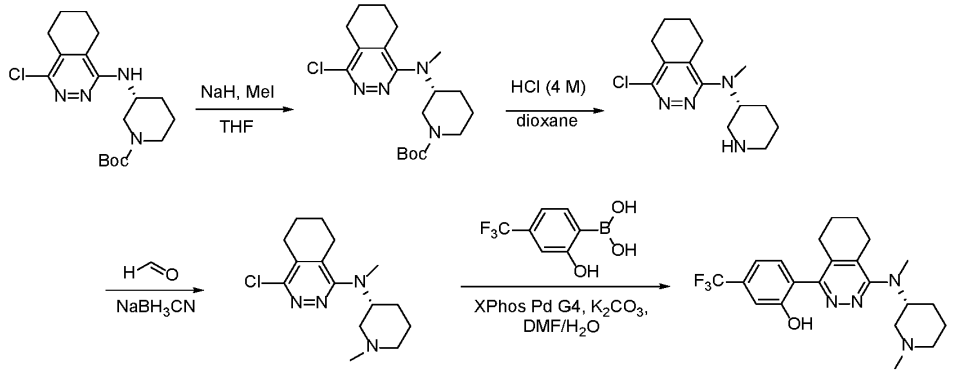
tert-Butyl (R)-3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)amino)piperidine-1-carboxylate (106 mg, 0.21 mmol), DCM (0.8 mL), and TFA (0.2 mL) were stirred at room temperature for 1 hour. Volatiles were removed by nitrogen stream. This mixture was then partitioned between aqueous NaOH and DCM. The DCM layer was dried over $MgSO_4$ and was filtered. (R)-2-(4-(piperidin-3-ylamino)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (89 mg, 93%) was obtained from the filtrate as an off-white solid. MS *m/z* 407.3 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 37.36 (d, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.15 (s, 1H), 4.26-4.32 (m, 1H), 3.41-3.46 (m, 1H), 3.05-3.10 (m, 1H), 2.60-2.83 (m, 6H), 2.11-2.16 (m, 1H), 1.87-1.93 (m, 3H), 1.59-1.80 (m, 6H). Three exchangeable protons are not seen.

Step 3: (R)-2-(4-((1-Methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol

(R)-2-(4-(Piperidin-3-ylamino)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (30 mg, 0.074 mmol), sodium triacetoxyborohydride (30 mg, 0.14 mmol), and DCM (0.5 mL) were stirred at room temperature. Aqueous formaldehyde (1.28 M, 0.1 mL, 0.13 mmol) was added dropwise. This was stirred vigorously at room temperature for 15 minutes. The mixture was partitioned between aqueous K_2CO_3 and DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by silica (0-70% MeON in DCM) yielded (R)-2-(4-((1-methylpiperidin-3-yl)amino)-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (21 mg, 68%) as a white solid. MS *m/z* 421.9 $[M+H]^+$; ^1H NMR (MeOH-d4) δ: 7.36 (d, J = 8 Hz 1H), 7.22 (d, J = 8 Hz 1H), 7.15 (s, 1H), 4.38-4.43 (m, 1H), 3.08-3.20 (m, 1H), 2.80-2.84 (m, 2H), 2.65-2.79 (m, 1H), 2.58-2.62 (m, 2H), 2.25-2.41 (m, 5H), 1.95-2.05 (m, 1H), 1.83-1.95 (m, 3H), 1.55-1.80 (m, 6H). Two exchangeable protons are not seen.

Example 13

Preparation of Compound I-47



Step 1. tert-Butyl (3R)-3-[(4-chloro-5, 6, 7, 8-tetrahydrophthalazin-1-yl)-methyl-amino] piperidine-1-carboxylate

To a solution of tert-butyl (3R)-3-[(4-chloro-5, 6, 7, 8-tetrahydrophthalazin-1-yl)amino] piperidine-1-carboxylate (prepared according to the procedure of Intermediate 19a, 1.3 g, 3.5 mmol) in 15 mL THF was added sodium hydride (218 mg, 5.4 mmol, 60 mass%) at 0 °C. The mixture was stirred at rt for 1 h. Then iodomethane (774 mg, 5.4 mmol) was added and the reaction was stirred at rt for 16 h, monitored by TLC and LCMS. After reaction, the mixture was quenched by water and extracted with EA. The combined organic layers was evaporated to dryness in vacuum. The residue was purified by column chromatography (0-20% EA in PE) to afford tert-butyl (3R)-3-[(4-chloro-5, 6, 7, 8-tetrahydrophthalazin-1-yl)-methyl-amino] piperidine-1-carboxylate (500 mg, 37% Yield) as a light yellow solid. MS *m/z* 381.2[M+H]$^+$.

Step 2. 4-Chloro-N-methyl-N-[(3R)-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine

To a solution of tert-butyl (3R)-3-[(4-chloro-5, 6, 7, 8-tetrahydrophthalazin-1-yl)-methyl-amino] piperidine-1-carboxylate (500 mg, 1.3 mmol) in 4 mL DCM was added HCl (2 mL, 4M in dioxane). This mixture was stirred at r.t for 3 h, monitored by TLC and LCMS. The solution was concentrated to give crude 4-chloro-N-methyl-N-[(3R)-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine (350 mg, 95% Yield) as a light yellow solid. MS *m/z* 281.2 [M+H]$^+$.

Step 3. 4-Chloro-N-methyl-N-[(3R)-1-methyl-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine

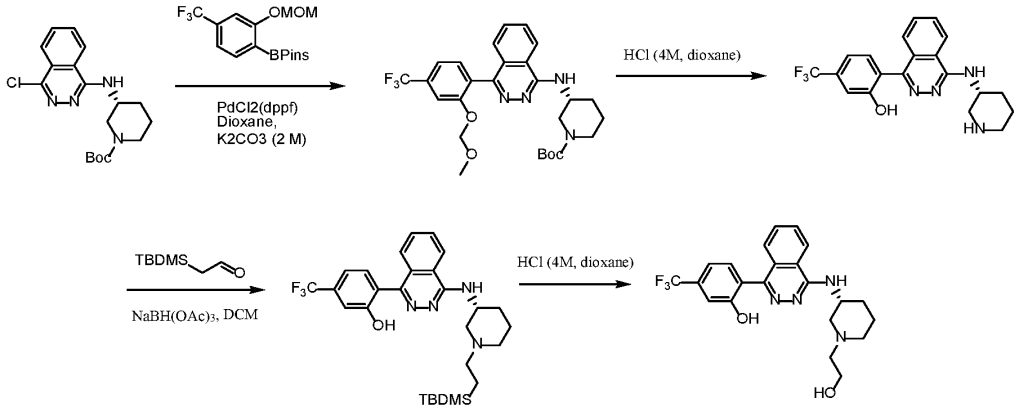
To a solution of 4-chloro-N-methyl-N-[(3R)-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine (5, 350 mg, 1.25 mmol) and formaldehyde (50 mg, 1.67 mmol) in MeOH (5 mL) was added sodium cyanoborohydride (86 mg, 1.37 mmol). This mixture was stirred at r.t for 16 h, monitored by TLC and LCMS. After reaction, the mixture was quenched by $NH_3 H_2O$ (7 mol/L in MeOH) and stirred at r.t for 1 h. The solution was concentrated and purified by column chromatography (0-5% MeOH in DCM) to afford 4-chloro-N-methyl-N-[(3R)-1-methyl-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine (200 mg, 54% Yield). MS *m/z* 295.1$[M+H]^+$.

Step 4. 2-[4-[Methyl-[(3R)-1-methyl-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol

To a solution of 4-chloro-N-methyl-N-[(3R)-1-methyl-3-piperidyl]-5, 6, 7, 8-tetrahydrophthalazin-1-amine (100 mg, 0.34 mmo) in 2 mL DMF and 0.5 mL H_2O was added [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (80 mg, 0.39 mmol), XPhos Pd G4 (30 mg, 0.03 mmol) and potassium carbonate (94 mg, 0.68 mmol). The mixture was stirred at 90 °C under N_2 atmosphere for 16 h, monitored by TLC and LCMS. After reaction, the mixture was concentrated and purified by prep-HPLC to give 2-[4-[methyl-[(3R)-1-methyl-3-piperidyl]amino]-5, 6, 7, 8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (30 mg, 21% Yield) as a light yellow solid. MS *m/z* 421.0 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD-d4) δ: 7.36 (d, *J* = 8 Hz, 1H), 7.24 (d, *J* = 8 Hz, 1H), 7.17 (s, 1H), 3.58-3.54 (m, 1H), 3.13-3.09 (m, 1H), 2.93-2.91 (m, 4H), 2.74-2.73 (m, 2H), 2.54-2.52 (m, 2H), 2.42-2.39 (m, 4H), 2.08-2.06 (m, 1H), 1.97-1.55 (m, 8H).

Example 14

Preparation of Compounds I-20 and I-48



Step 1. tert-Butyl (3R)-3-[[4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]piperidine-1-carboxylate

A mixture of tert-butyl (3R)-3-[(4-chlorophthalazin-1-yl)amino]piperidine-1-carboxylate (prepared according to the procedure of Intermediate 19a, 120 mg, 0.33 mmol, 1.0 eq.), 2-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (143 mg, 0.43 mmol, 1.3 eq.) and Xphos Pd G3 (23 mg, 0.08 eq.) in K_2CO_3 (2M) in H_2O (0.5 mL, 3.0 eq.) and dioxane (1.3 mL) were bubbled with Ar. The sealed tube was then heated at 90°C for 12 hr. After cooling, the reaction was diluted with EtOAc and water. The organic phase was washed with H_2O followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-50% EtOAc in DCM to provide tert-butyl (3R)-3-[[4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]piperidine-1-carboxylate (141 mg, 80 % yield). MS *m/z* 533.8 $[M+H]^+$.

Step 2. 2-[4-[[(3R)-3-Piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol hydrochloride

tert-Butyl (3R)-3-[[4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]piperidine-1-carboxylate (55 mg, 0.10 mmol) was stirred in a solution of HCl (4 M in dioxane, 1 mL) at room temperature for 1 h. The organic volatiles were removed. The residue was triturated with diethyl ether and filtered to afford 2-[4-[[(3R)-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (39 mg, 89 % yield) as hydrochloride salt. MS *m/z* 389.7

$[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.73 (d, J=8.1 Hz, 1H), 8.31 (br t, J=7.5 Hz, 1H), 8.16 (t, J=7.7 Hz, 1H), 7.98 (br d, J=8.4 Hz, 1H), 7.71 (br d, J=8.1 Hz, 1H), 7.46 (br d, J=7.9 Hz, 1H), 7.39 (s, 1H), 4.62 (br d, J=4.4 Hz, 1H), 3.73-3.83 (m, 1H), 3.41-3.49 (m, 1H), 3.08-3.25 (m, 2H), 2.36 (br d, J=7.1 Hz, 1H), 2.20 (br dd, J=6.2, 3.9 Hz, 1H), 1.93-2.05 (m, 2H). 3 NHs and OH not observed.

Step 3. 2-[4-[[(3R)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol

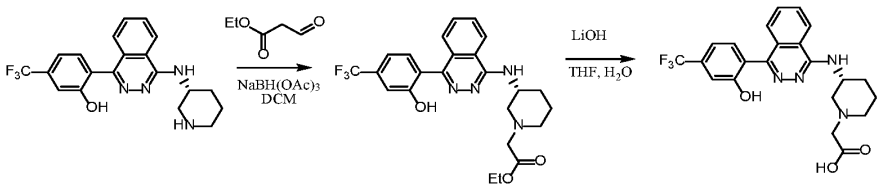
A mixture of 2-[4-[[(3R)-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (36 mg, 0.084 mmol, 1.0 eq.) hydrochloride, (tert-butyldimethylsilyloxy)acetaldehyde (18 mg, 0.092 mmol, 1.1 eq.) and sodium triacetoxyborohydride (55 mg, 3.0 eq.) in DIPEA (22 mg, 2.0 eq.) and DCM (0.6 mL) was stirred at rt for 15 mins. The reaction was diluted with DCM and $NaHCO_3$ (sat. aq.). The organic phase was washed with H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on basic alumina eluting with 0-10% MeOH in DCM to provide 2-[4-[[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (15 mg, 33 % yield). MS *m/z* 546.8 $[M+H]^+$.

Step 4. 2-[4-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol formic acid salt

2-[4-[[(3R)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (15 mg, 0.027 mmol) was stirred in a solution of HCl (4 M in dioxane, 1 mL) at room temperature for 1 h. The organic volatiles were removed. The residue was then purified on prep-HPLC with 5-50% ACN in water with 0.1% formic acid to provide 2-[4-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]phthalazin-1-yl]-5-(trifluoromethyl)phenol (8 mg, 67 % yield) as formic acid salt. MS *m/z* 433.3 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 8.43 (s, 1H, formic acid-H), 8.22 (br d, J=8.4 Hz, 1H), 7.80 (t, J=6.9 Hz, 1H), 7.72 (br t, J=7.6 Hz, 1H), 7.52 (br d, J=7.9 Hz, 1H), 7.43 (br d, J=7.8 Hz, 1H), 7.21 (br d, J=8.0 Hz, 1H), 7.15 (s, 1H), 4.54 (br s, 1H), 3.71 (br t, J=5.0 Hz, 2H), 3.35-3.50 (m, 1H), 2.93-3.06 (m, 1H), 2.72-2.89 (m, 2H), 2.52-2.72 (m, 2H), 1.97-2.08 (m, 1H), 1.84-1.96 (m, 1H), 1.66-1.84 (m, 2H). NH and 2 OH not observed.

Example 15

Preparation of Compounds I-65 and I-98



Step 1. Ethyl (R)-2-(3-((4-(2-hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)amino)piperidin-1-yl)acetate

A mixture of 2-[4-[[(3R)-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol hydrochloride (Example 14, step 3, 50 mg, 0.11 mmol) and sodium perborate tetrahydrate (31 mg) in DIPEA (29 mg, 2.0 eq.) and DCM (0.5 mL) was stirred for 15 mins, followed by addition of ethyl 3-oxopropanoate (17 mg, 1.5 eq.) and $NaBH(OAc)_3$ (71 mg, 3.0 eq.). After 15 mins, the reaction was quenched by dilution with DCM and $NaHCO_3$ (sat.). The organic phase was washed with H_2O followed by brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-20% MeOH (with NH_4OH as modifier) in DCM to provide 2-[4-[[(3R)-1-cyclobutyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (45 mg, 88% yield). MS *m/z* 475.3 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 8.36 (d, J=8.3 Hz, 1H), 7.88-7.93 (m, 1H), 7.82 (t, J=7.6 Hz, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.9 Hz, 1H), 7.31 (br d, J=8.3 Hz, 1H), 7.26 (s, 1H), 4.62 (br s, 1H), 4.22 (q, J=7.1 Hz, 2H), 3.47-3.54 (m, 1H), 3.04 (br d, J=10.6 Hz, 1H), 2.58-2.76 (m, 3H), 1.79-2.00 (m, 3H), 1.74 (br d, J=6.1 Hz, 1H), 1.24-1.35 (t, J=6.9 Hz, 3H), 1.20 (t, J=6.9 Hz, 1H). NH and OH not observed.

Step 2. (R)-2-(3-((4-(2-Hydroxy-4-(trifluoromethyl)phenyl)phthalazin-1-yl)amino)piperidin-1-yl)acetic acid

To a solution of ethyl 2-[(3R)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]-1-piperidyl]acetate (40 mg, 0.084) in THF (2 mL) was added H_2O (0.5 mL), followed by LiOH (2 mg, 1.0 eq.). After stirring at rt for 2-3 hr, the reaction mixture was neutralized by citric acid to pH~7, then extracted with EtOAc. The organic volatiles were removed. The residue was then purified on prep-HPLC with 5-30% ACN in water with 0.1% formic acid to provide 2-[(3R)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl]amino]-1-piperidyl]acetic acid (5 mg, 13% yield) as formic acid salt. MS *m/z* 447.2 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 8.33 (d,

J=8.1 Hz, 1H), 7.89-7.97 (m, 1H), 7.82-7.89 (m, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.29-7.36 (m, 1H), 7.24-7.29 (m, 1H), 4.77-4.87 (m, 1H), 3.78-3.96 (m, 1H), 3.58-3.75 (m, 3H), 3.03-3.24 (m, 2H), 2.22-2.34 (m, 1H), 2.12-2.22 (m, 1H), 2.04 (br dd, J=11.3, 3.5 Hz, 1H), 1.89 (br d, J=10.3 Hz, 1H). NH and OH not observed.

The compounds below were prepared according to the procedure of Example 15 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-21	MS *m/z* 390.1 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 8.52 (br d, J=8.0 Hz, 1H), 7.90-8.09 (m, 2H), 7.72 (br d, J=8.1 Hz, 1H), 7.56 (br d, J=7.8 Hz, 1H), 7.24-7.43 (m, 2H),5.88 (br s, 1H), 3.81 (br d, J=11.6 Hz, 1H), 3.62 (br d, J=12.9 Hz, 1H), 3.43 (br d, J=12.1 Hz, 1H), 3.28-3.35 (m, 2H), 2.15-2.40 (m, 3H), 1.97 (br d,J=13.9 Hz, 1H).
I-22	MS *m/z* 404.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.45-8.54 (m, 1H), 8.38-8.43 (m, 1H), 7.87-8.04 (m, 2H), 7.70 (d, J=8.0 Hz, 1H), 7.55 (d, J=7.9 Hz, 1H), 7.27-7.41(m, 2H), 5.90 (br s, 1H), 3.84 (br s, 1H), 3.55 (br d, J=12.5 Hz, 1H), 3.41-3.50 (m, 1H), 3.07-3.31 (m, 1H), 2.90 (s, 3H), 2.20-2.40 (m, 2H), 2.11 (br d, J=10.9 Hz, 1H), 1.91-2.05 (m, 1H)
I-29	MS *m/z* 404.2 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 8.37 (br d, J=8.1 Hz, 1H), 8.23 (s, 2H), 7.90 (t, J=7.0 Hz, 1H), 7.80-7.85 (m, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.43 (d, J=7.9 Hz, 1H), 7.13-7.27 (m, 2H), 5.77 (br s, 1H), 3.68 (br s, 1H), 3.32-3.53 (m, 1H), 3.24-3.34 (m, 1H), 3.06 (br t, J=10.1 Hz, 1H), 2.77 (s, 3H), 2.09-2.27 (m, 2H), 2.00 (br d, J=12.9 Hz, 1H), 1.80-1.94 (m, 1H).
I-35	MS *m/z* 390.7 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 9.73 (s, 1H), 8.90 (d, J=5.5 Hz, 1H), 8.35 (s, 1H), 7.59 (d, J=7.9 Hz, 1H), 7.52 (d, J=5.6 Hz, 1H), 7.35 (br d, J=7.9 Hz, 1H), 7.30 (s, 1H), 4.64-4.81 (m, 1H), 3.83 (br d, J=10.1 Hz, 1H), 3.35-3.50 (m, 1H), 3.11 (br t, J=11.0 Hz, 2H), 2.34 (br s, 1H), 2.19 (br s, 1H), 1.97 (br t, J=9.6 Hz, 2H).
I-43	MS *m/z* 418.2 $[M+H]^+$, ^1H NMR (METHANOL-d4) δ: 9.73 (s, 1H), 8.91 (d, J=5.6 Hz, 1H), 8.34 (br s, 2H), 7.59 (d, J=7.9 Hz, 1H), 7.52 (d, J=5.6 Hz, 1H), 7.36 (d, J=7.9 Hz, 1H), 7.30 (s, 1H), 4.71-4.82 (m, 1H), 3.89-4.04 (m, 1H), 3.48-3.68 (m, 1H), 3.21-3.28 (m, 2H), 2.94-3.17 (m, 2H), 2.19-2.40 (m, 2H), 1.99 (br d, J=10.6 Hz, 2H), 1.40 (t, J=7.3 Hz, 3H)
I-45	MS *m/z* 407.8 $[M+H]^+$; ^1H NMR (MeOH-d4) d: 7.31 (d, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.18 (s, 1H), 4.29-4.34 (m, 1H), 3.41-3.47 (m, 1H), 3.05-3.11 (m, 1H), 2.65-2.82 (m, 4H), 2.12-2.16 (m, 1H), 1.98 (t, J = 7 Hz, 2H), 1.90-1.95 (m, 1H), 1.63-1.80 (m, 2H), 1,06 (s, 6H). Three exchangeable protons are not seen.
I-46	MS *m/z* 421.9 $[M+H]^+$; ^1H NMR (MeOH-d4) d: 7.31 (d, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.18 (s, 1H), 4.40-4.47 (m, 1H), 3.08-3.20 (m, 1H), 2.76-2.83 (m, 3H), 2.28-2.43 (m, 5H), 1.95-2.10 (m, 3H), 1.83-1.93 (m, 1H), 1.68-1.81 (m, 1H), 1.50-1.65 (m, 1H), 1.06 (s, 6H). Two exchangeable protons are not seen.

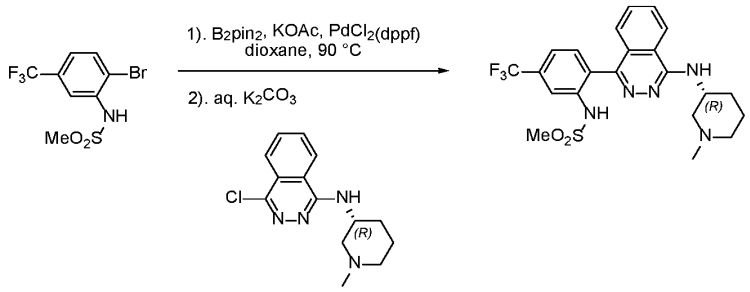
Compound	Spectral Data
I-53	MS *m/z* 405.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H, formic acid), 8.15 (d, J=8.3 Hz, 1H), 7.95 (t, J=7.6 Hz, 1H), 7.86 (t, J=7.6 Hz, 1H), 7.65 (d, J=8.3 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.33 (br d, J=8.0 Hz, 1H), 7.27 (s, 1H), 4.71-4.84 (m, 1H), 4.13-4.23 (m, 1H), 3.44-3.54 (m, 1H), 3.13-3.29 (m, 2H, overlapped with CD_3OD), 3.02 (br dd, J=12.6, 5.9 Hz, 1H), 2.36-2.44 (m, 1H), 2.05 (dt, J=13.4, 6.7 Hz, 1H). NH and OH not observed.
I-55	MS *m/z* 434.5 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.74 (s, 1H), 8.85 (d, J=5.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.49 (d, J=5.8 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.26 (s, 1H), 4.59-4.68 (m, 1H), 3.68-3.81 (m, 2H), 3.10-3.24 (m, 1H), 2.52-2.75 (m, 3H), 2.46 (br s, 2H), 1.99-2.13 (m, 1H), 1.90 (br dd, J=8.4, 2.6 Hz, 1H), 1.72-1.83 (m, 2H), 1.16-1.21 (m, 1H), NH and OHs not observed.
I-63	MS *m/z* 419.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H, formic acid), 8.04 (br d, J=7.9 Hz, 1H), 7.82 (br t, J=7.5 Hz, 1H), 7.74 (br t, J=7.6 Hz, 1H), 7.53 (br d, J=8.1 Hz, 1H), 7.42 (br d, J=7.8 Hz, 1H), 7.12-7.25 (m, 2H), 4.68 (br s, 1H), 4.11 (br s, 1H), 3.25 (br s, 1H), 2.94-3.19 (m, 2H), 2.53-2.72 (m, 3H), 2.20 (br d, J=11.9 Hz, 1H), 1.93 (s, 1H), 1.65-1.89 (m, 1H). NH and OH not observed.
I-68	MS *m/z* 389.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.68 (s, 1H), 8.41 (s, 1H), 8.34 (d, J = 8.3 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.83 – 7.68 (m, 2H), 7.48 (dd, J = 16.6, 8.0 Hz, 2H), 7.34 – 7.23 (m, 2H), 3.73 – 3.54 (m, 2H), 3.23 – 3.10 (m, 2H), 3.08 – 2.99 (m, 1H), 2.97 – 2.89 (m, 1H), 2.86 – 2.73 (m, 1H), 2.10 – 1.93 (m, 1H), 1.81 – 1.58 (m, 1H).
I-83	MS *m/z* 405.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H, formic acid), 8.19 (br d, J=8.1 Hz, 1H), 7.79-7.85 (m, 1H), 7.74 (br t, J=7.5 Hz, 1H), 7.53 (br d, J=8.1 Hz, 1H), 7.43 (br d, J=7.9 Hz, 1H), 7.14-7.24 (m, 2H), 4.95 (br s, 1H), 4.27 (br s, 1H), 3.73 (br d, J=10.6 Hz, 1H), 3.17 (br s, 1H), 3.05 (br d, J=13.1 Hz, 1H), 2.80 (br t, J=11.4 Hz, 1H), 2.26 (br d, J=12.8 Hz, 1H), 1.97 (br t, J=13.1 Hz, 1H). NH and OH not observed.
I-84	MS *m/z* 419.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.32 (d, J=8.1 Hz, 1H), 7.91 (t, J=7.2 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 7.63 (d, J=8.3 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.32 (br d, J=7.8 Hz, 1H), 7.26 (s, 1H), 4.80 (s, 1H, overlapped with CD3OD), 4.03-4.15 (m, 1H), 2.64-2.90 (m, 3H), 2.32-2.49 (m, 4H), 2.14-2.29 (m, 1H), 1.76-1.91 (m, 1H). NH and OH not observed.
I-87	MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.24 (d, J = 8.2 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.07 – 2.79 (m, 4H), 2.76 – 2.67 (m, 1H), 2.54 (s, 3H), 2.23 – 2.11 (m, 1H), 1.86 – 1.73 (m, 1H).
I-101	MS *m/z* 434.5 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 9.74 (s, 1H), 8.85 (d, J=5.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.49 (d, J=5.8 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 7.26 (s, 1H), 4.59-4.68 (m, 1H), 3.68-3.81 (m, 2H), 3.10-3.24 (m, 1H), 2.52-2.75 (m, 3H), 2.46 (m, 2H), 1.99-2.13 (m, 1H), 1.90 (br dd, J=8.4, 2.6 Hz,1H), 1.72-1.83 (m, 2H), 1.16-1.21 (m, 1H)
I-110	MS *m/z* 390.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.00 – 8.91 (m, 2H), 8.55 (s, 1H), 8.11 (d, J = 5.7 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.9

Compound	Spectral Data
	Hz, 1H), 7.28 (s, 1H), 3.87 – 3.75 (m, 2H), 3.52 – 3.39 (m, 3H), 3.21 – 3.14 (m, 1H), 3.03 – 2.91 (m, 1H), 2.32 – 2.21 (m, 1H), 1.99 – 1.86 (m, 1H).
I-111	MS *m/z* 390.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.62 (d, J = 1.1 Hz, 1H), 8.88 (d, J = 5.7 Hz, 1H), 8.45 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 5.7 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.29 – 7.24 (m, 1H), 3.90 – 3.77 (m, 2H), 3.55 – 3.41 (m, 2H), 3.37 – 3.30 (m, 1H), 3.24 – 3.16 (m, 1H), 3.05 – 2.93 (m, 1H), 2.35 – 2.20 (m, 1H), 2.02 – 1.88 (m, 1H).
I-112	MS *m/z* 404.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.66 – 9.57 (m, 1H), 8.86 (d, J = 5.7 Hz, 1H), 8.55 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 5.8 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.27 (s, 1H), 3.82 – 3.73 (m, 2H), 3.25 – 3.18 (m, 1H), 3.15 – 2.90 (m, 4H), 2.69 (s, 3H), 2.33 – 2.19 (m, 1H), 1.96 – 1.81 (m, 1H).
I-151	MS *m/z* 421.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.30 (d, J=8.3 Hz, 1H), 7.90 (t, J=7.2 Hz, 1H), 7.80-7.85 (m, 1H), 7.62 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.26 (s, 1H), 5.06 (br s, 1H), 4.91-4.97 (m, 1H), 3.23-3.29 (m, 1H), 2.94-3.06 (m, 1H), 2.35-2.52 (m, 5H), 2.22-2.30 (m, 1H), 1.84-2.05 (m, 1H). OH and NH not observed.
I-164	MS *m/z* 421.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.28-8.32 (m, J=8.3 Hz, 1H), 7.88-7.95 (m, 1H), 7.78-7.86 (m, 1H), 7.61-7.67 (m, J=8.1 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.29-7.35 (m, 1H), 7.23-7.29 (m, 1H), 5.05-5.12 (m, 1H), 4.93-5.00 (m, 1H), 3.23-3.29 (m, 1H), 2.94-3.06 (m, 1H), 2.35-2.52 (m, 5H), 2.22-2.30 (m, 1H), 1.84-2.05 (m, 1H). OH and NH not observed.
I-235	MS *m/z* 468.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J = 5.8 Hz, 1H), 8.81 (s, 1H), 8.35 (d, J = 5.88 Hz, 1H), 8.22 (s, 1H, formic acid), 7.87 – 7.80 (m, 2H), 7.74 (s, 1H), 7.66 (s, 1H), 7.38 (t, J = 73.67 Hz, 1 H), 4.49 – 4.34 (m, 1H), 3.22 – 3.13 (m, 1H), 2.89 – 2.78 (m, 1H), 2.40 (q, J = 7.3 Hz, 2H), 2.08 – 1.88 (m, 3H), 1.81 – 1.67 (m, 1H), 1.65 – 1.42 (m, 2H), 1.02 (t, J = 7.1 Hz, 3H)
I-278	MS *m/z* 422.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1 H), 8.85 (d, J = 5.63 Hz, 1 H), 8.23 (s, 1 H, formic acid), 7.69 (d, J = 8.63 Hz, 1 H), 7.56 (d, J = 7.88 Hz, 1 H), 7.35- 7.27 (m, 3 H), 5.02 (d, J = 45.53 Hz, 1 H), 4.84 - 4.72 (m, 1 H), 3.11 (dd, J=11.01, 2.00 Hz, 1 H), 2.99 - 2.87 (m, 1 H), 2.34 – 2.20 (m, 4 H), 2.20 - 2.11 (m, 1 H), 2.09 - 1.98 (m, 1 H), 1.94 - 1.64 (m, 1 H). 1H not observed (OH).
I-279	MS *m/z* 472.2 [M-H]-; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.70 (s, 1H), 8.85 (d, J = 5.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.30 - 7.26 (m, 1H), 4.68 - 4.57 (m, 1H), 4.01 (br dd, J = 3.1, 11.3 Hz, 2H), 3.49 - 3.35 (m, 3H), 2.94 (br d, J = 11.0 Hz, 1H), 2.77 - 2.57 (m, 1H), 2.57 - 2.36 (m, 2H), 2.21 - 2.08 (m, 1H), 1.96 - 1.84 (m, 3H), 1.84 - 1.56 (m, 4H); NH and OH wasn't observed
I-280	MS *m/z* $[M+H]^+$; 422.0; ^1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H), 8.85 (d, J = 5.75, 1H), 8.20 (s, 1H, formic acid), 7.70 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.35 – 7.25 (m, 3H), 5.02 (d, J = 46.4 Hz, 1H), 4.85 – 4.72 (m, 1H), 3.15 – 3.06 (m, 1H), 3.01 – 2.89 (m, 1H), 2.34 – 2.20 (m, 4H), 2.20 – 2.11 (m, 1H), 2.10 – 1.96 (m, 1H), 1.94 – 1.64 (m, 1H). 1H not observed (OH)

Compound	Spectral Data
I-311	MS *m/z* 440.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 9.84 – 9.68 (m, 1H), 8.90 (d, J = 5.6 Hz, 1H), 8.55 (s, 1H), 7.79 (s, 2H), 7.71 (s, 1H), 7.40 (d, J = 5.6 Hz, 1H), 7.15 – 6.65 (m, 1H), 4.79 – 4.48 (m, 2H), 3.71 (br d, J = 12.3 Hz, 1H), 3.11 – 2.92 (m, 2H), 2.29 (br s, 1H), 2.11 (br s, 1H), 2.00 – 1.78 (m, 2H). NH not observed
I-312	MS *m/z* 494.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 9.85 – 9.65 (m, 1H), 8.97 – 8.77 (m, 1H), 7.78 (s, 2H), 7.69 (s, 1H), 7.36 (d, J = 5.6 Hz, 1H), 7.12 – 6.66 (m, 1H), 4.73 – 4.56 (m, 1H), 3.25 – 3.12 (m, 1H), 2.99 – 2.87 (m, 1H), 2.83 – 2.71 (m, 1H), 2.29 – 2.07 (m, 5H), 2.06 – 1.94 (m, 2H), 1.93 – 1.84 (m, 1H), 1.83 – 1.65 (m, 4H). NH not observed

Example 16

Preparation of Compound I-124



A mixture of *N*-[2-bromo-5-(trifluoromethyl)phenyl]-methanesulfonamide (prepared according to EP1837329, 2007, A1, 0.058 g, 0.18 mmol), B_2pin_2 (0.058 g, 0.23 mmol), KOAc (0.054 g, 0.055 mmol) and $Pd(dppf)Cl_2$ (0.005 g, 0.009 mmol) was evacuated and backfilled with Ar (3x) before being dissolved in dioxane (0.9 mL). The reaction was heated to 90 °C for 18 h, then cooled and to which was added 4-chloro-*N*-[(3*R*)-1-methyl-3-piperidyl]phthalazin-1-amine (Intermediate 19a, 0.048 g, 0.17 mmol), $PdCl_2(dppf)$ (0.0055 g, 0.007 mmol), and K_2CO_3 (2 M, 0.28 mL, 0.55 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 3 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) then reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.018 g, 19%). MS *m/z* 480.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ: 8.46 (s, 1 H, formic acid), 8.36 (d, *J* = 8.50 Hz, 1 H), 8.04 – 7.99 (m, 1 H), 7.99 – 7.91 (m, 1 H), 7.91 – 7.82 (m, 1 H), 7.74 – 7.59 (m, 3 H), 4.76 - 4.58 (m, 1 H), 2.90 (s, 3 H), 2.79 (s, 3 H), 2.59 – 2.43 (m, 1 H), 2.31 - 2.06 (m, 2 H), 2.02 – 1.77 (m, 2 H), 1.74

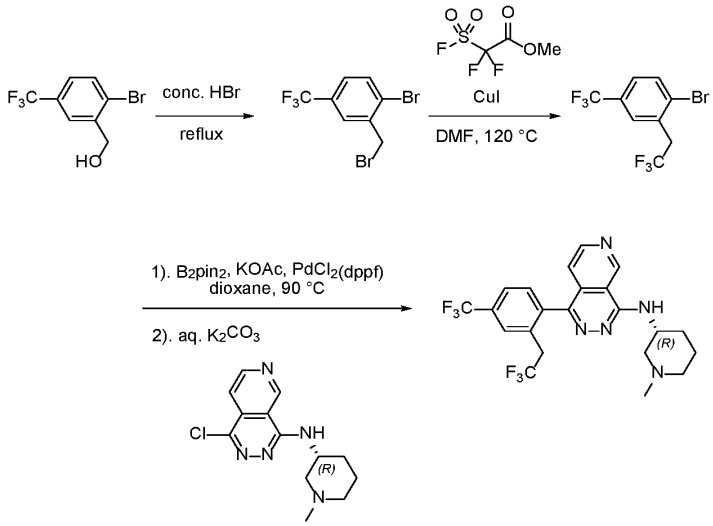
– 1.63 (m, 1 H), 0.84 - 0.66 (m, 2 H). 2Hs not observed (2 NH).

The compounds below were prepared according to the procedure of Example 16 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-126	MS *m/z* 444.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ: 8.43 - 8.32 (m, 2 H), 8.22 (s, 1 H, formic acid), 7.95 (t, *J* = 7.63 Hz, 1 H), 7.85 (t, *J* = 8.63 Hz, 1 H), 7.74 – 7.65 (m, 2 H), 7.55 (d, *J* = 8.25 Hz, 1 H), 4.76 - 4.65 (m, 1 H), 3.89 – 3.76 (m, 1 H), 3.50 – 3.39 (m, 1 H), 3.14 – 2.98 (m, 2 H), 2.89 (s, 3 H), 2.30 – 2.14 (m, 2 H), 2.05 – 1.86 (m, 2 H), 1.79 (s, 3 H). 2Hs not observed (2 NH)
I-204	MS *m/z* 455.9 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.78 (d, J=0.8 Hz, 1H), 8.92 (d, J=5.8 Hz, 1H), 8.31 (d, J=7.5 Hz, 1H), 7.91 (d, J=7.3 Hz, 1H), 7.66 (t, J=71.5 Hz, 1H), 7.50 (dd, J=5.8, 0.8 Hz, 1H), 4.68-4.76 (m, 1H), 3.43-3.54 (m, 1H), 3.01-3.09 (m, 1H), 2.64-2.77 (m, 2H), 2.63 (s, 3H), 2.15-2.27 (m, 1H), 2.01-2.12 (m, 1H), 1.77-1.93 (m, 2H); 1H not observed (NH).

Example 17

Preparation of Compound I-214



Step 1: 1-Bromo-2-(bromomethyl)-4-trifluoromethyl)benzene

[2-Bromo-5-(trifluoromethyl)phenyl]methanol (1.70 g, 6.67 mmol) in conc. HBr (8 mL) was heated to reflux for 2 h. The reaction was cooled to rt and extracted with DCM. The combined organic extracts were washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 10%) gave a colorless oil (1.12 g, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 2H),

7.43 (dd, J = 8.38 Hz, 2.00 Hz, 1H), 4.62 (s, 2 H).

Step 2. 1-Bromo-2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)benzene

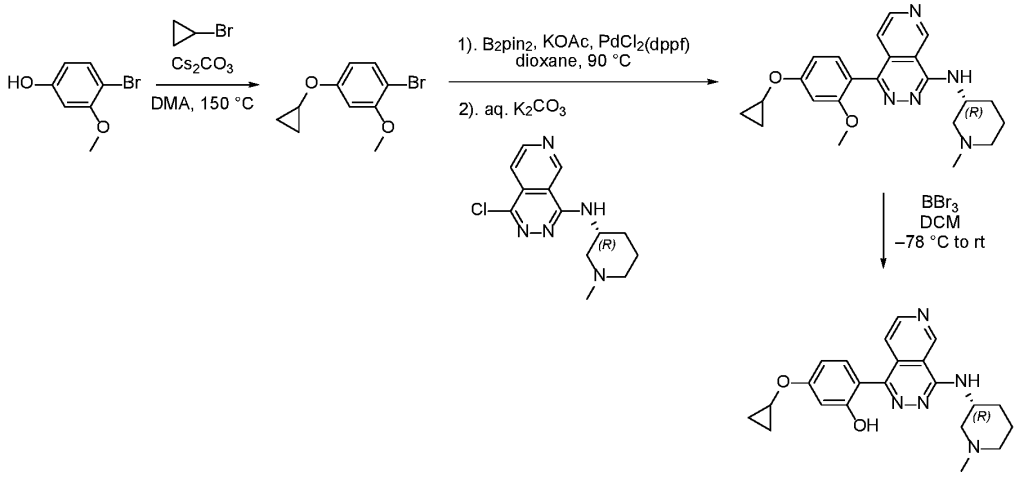
To a solution of 1-bromo-2-(bromomethyl)-4-(trifluoromethyl)benzene (1.20 g, 3.77 mmol) in DMF (8.4 mL) was added CuI (1.80 g, 9.44 mmol), and the solution was sparged with Ar. To this solution was added difluoro-fluorosulfonyl-acetic acid methyl ester (1.20 mL, 9.44 mmol), and the resulting reaction mixture was heated at 120 °C for 4 h The reaction mixture was cooled to 0 °C, diluted with EtOAc (60ml) and stirred for 10 minutes at 0 °C. A solution of ammonium hydroxide (conc., 6 mL) was added dropwise and the mixture was stirred as it warmed to rt. EtOAc (100 mL) and water (50 mL) were added and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 10%) gave a yellow oil (0.215 g, 19%).

Step 3: (*R*)-*N*-(1-Methylpiperidin-3-yl)-1-(2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)-phenyl)pyrido[3,4-*d*]pyridazin-4-amine formic acid salt.

The titled compound was prepared according to the procedure of 16 . MS m/z 470.5 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H, formic acid), 8.03 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 9.26 Hz, 1H), 7.22 (d, J = 5.8 Hz, 1H), 4.56 – 4.43 (m, 1H), 4.11 – 3.59 (m, 2H), 3.16 – 3.05 (m, 1H), 2.78 – 2.69 (m, 1H), 2.23 (s, 3H), 2.08 – 1.85 (m, 3H), 1.83 – 1.71 (m, 1H), 1.69 – 1.55 (m, 1H), 1.55 – 1.39 (m, 1H)

Example 18

(Preparation of Compound I-237



Step 1: 1-Bromo-4-(cyclopropoxy)-2-methoxy-benzene

A solution of 4-bromo-3-methoxy-phenol (0.750 g, 53.69 mmol) in DMA (10.7 ml) was added Cs_2CO_3 (3.01 g, 9.23 mmol). The mixture was stirred for 5 min before bromocyclopropane (1.48 mL, 18.5 mmol) was added. The mixture was heated to 150 °C for 24 h. The reaction was diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 20%) gave a light-yellow oil (0.591 g, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.63 Hz, 2H), 6.67 – 6.60 (m, 2H), 6.60 – 6.56 (m, 1H), 3.87 (s, 1 H), 3.77 – 3.70 (m, 1 H), 0.82 – 0.76 (m, 4 H).

Step 2. 5-(Cyclopropoxy)-2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrido[3,4-*d*]pyridazin-1-yl]phenol

5-(Cyclopropoxy)-2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]phenol was prepared according to the procedure of Example 16 (0.089 g, 54%). MS *m/z* 406.6 $[M+H]^+$.

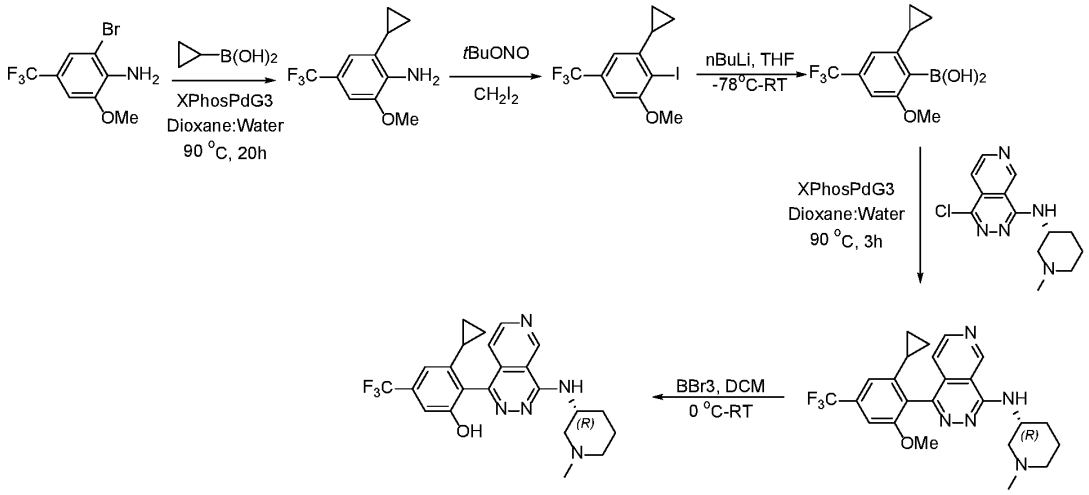
Step 3: (*R*)-5-Cyclopropoxy-2-(4-((1-methylpiperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)phenol formic acid salt.

A solution 5-(cyclopropoxy)-2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]phenol (0.089 g, 0.22 mmol) in DCM (1.1 mL) was cooled to –78 °C and BBr_3 (1.0 M in DCM, 1.8 ml, 1.8 mmol) was added. The reaction was stirred at –78 °C for 30 min and

let warm to rt. The reaction was then stirred for 1.5 h before quenching by the addition of MeOH (0.5 mL). The mixture was diluted with DCM (20 mL), stirred 10 min. Sat. $NaHCO_3$ (1.0 mL) was added and vigorously stirred for 15 min. The layers were separated, and the aqueous phase was extracted with DCM. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a tan solid (0.009 g, 10%). MS *m/z* 392.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.71 (s, 1H), 8.88 (d, *J* = 6.75 Hz, 1H), 8.31 (s, 1H, formic acid), 7.81 (d, *J* = 7.88 Hz, 1H), 7.38 (d, *J* = 6.00 Hz, 1H), 7.25 (d, *J* = 8.51 Hz, 1H), 6.72 (d, *J* = 3.00 Hz, 1H), 6.67 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.09 – 4.96 (m, 1H), 3.88 – 3.77 (m, 2H), 3.68 – 3.41 (m, 2H), 3.26 – 3.16 (m, 3H), 2.27 – 2.11 (m, 3H), 2.11 – 1.96 (m, 1H), 1.74 – 1.57 (m, 1H), 0.88 – 0.77 (m, 2H), 0.75 – 0.68 (m, 2H). 1H not observed (OH).

Example 19

Preparation of Compound I-274



Step 1: 2-Cyclopropyl-6-methoxy-4-(trifluoromethyl)aniline

To a vial was added 2-bromo-6-methoxy-4-(trifluoromethyl)aniline (5.1 g, 19 mmol), cyclopropylboronic acid (1.5 eq., 2.4 g, 28 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (0.1 eq., 1.6 g, 1.9 mmol), and potassium carbonate (3 eq., 7.8 g, 57 mmol) under Ar. 1,4-Dioxane:water (4:1) (100 mass%) was added and the resulting mixture was warmed to 90°C, and stirred for 20 h. The crude material was partitioned between EtOAc and brine. The brine was extracted with

EtOAc (2x). The organic phase was concentrated and purified by column chromatography, eluting with 0-100% DCM/MeOH to afford 2-cyclopropyl-6-methoxy-4-(trifluoromethyl)aniline (2.6 g, 60% Yield), MS *m/z* 231.9 $[M+H]^+$

Step 2. 1-Cyclopropyl-2-iodo-3-methoxy-5-(trifluoromethyl)benzene

To a vial was added 2-cyclopropyl-6-methoxy-4-(trifluoromethyl)aniline (1.0 g, 4.3 mmol), acetonitrile (0.2 M, 22 mL), , and tert-butyl nitrite (3 eq., 1.5 mL, 13 mmol). Next, at 0°C diiodomethane (1.5 eq., 0.52 mL, 6.5 mmol) was added dropwise and the resulting mixture was warmed to 60°C, and stirred for 6 h. The crude material was partitioned between EtOAc and brine and the brine was extracted with EtOAc (2x). The organic phase was concentrated and purified by column chromatography, eluting with 0-100% Hexane/ EtOAc to afford 1-cyclopropyl-2-iodo-3-methoxy-5-(trifluoromethyl)benzene (1-cyclopropyl-2-iodo-3-methoxy-5-(trifluoromethyl)benzene (390 mg, 26% Yield). ^{1}H NMR (CHLOROFORM-d) δ: 7.48-7.57 (s, 1H), 6.85 (s, 1H), 3.96-4.01 (s, 3H), 2.16 (m, 1H), 1.11 (m, 2H), 0.72 (m, 2H).

Step 3: [2-Cyclopropyl-6-methoxy-4-(trifluoromethyl)phenyl]boronic acid

To a solution of 1-cyclopropyl-2-iodo-3-methoxy-5-(trifluoromethyl)benzene (390 mg, 1.14 mmol) in THF (0.2 M, 5.7 ml) was added n-BuLi (2.5 M in hexane, 1.5 eq. 0.68 ml) dropwise. The resulting mixture was stirred at -78°C for 30 minutes, after which triisopropyl borate (2 eq., 0.52 ml) was added. The mixture was stirred at -78°C for another 10 minutes, then allowed to warm to RT and stirred for 2 h. The mixture was partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc (x3). The combined organic phase was concentrated which was used for the next step without further purification.

Step 4: 1-[2-Cyclopropyl-6-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine

To a mixture of 1-chloro-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (100 mg, 0.36 mmol), [2-cyclopropyl-6-methoxy-4-(trifluoromethyl)phenyl]boronic acid (1 eq., 0.36 mmol), (2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (0.1 eq., 0.036 mmol) and potassium carbonate (3 eq., 1.08 mmol) was added 1,4-dioxane: water (4:1) (0.25 M, 1.4 ml) under Ar. The resulting mixture was warmed to 90°C and stirred for 3 h. The mixture was then partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc (x2). The combined organic phase was concentrated and the residue was purified by column chromatography, eluting with 0-50%

DCM/MeOH to afford 1-[2-cyclopropyl-6-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (144 mg, 0.31 mmol, 87% Yield) MS *m/z* 458.9 $[M+H]^+$.

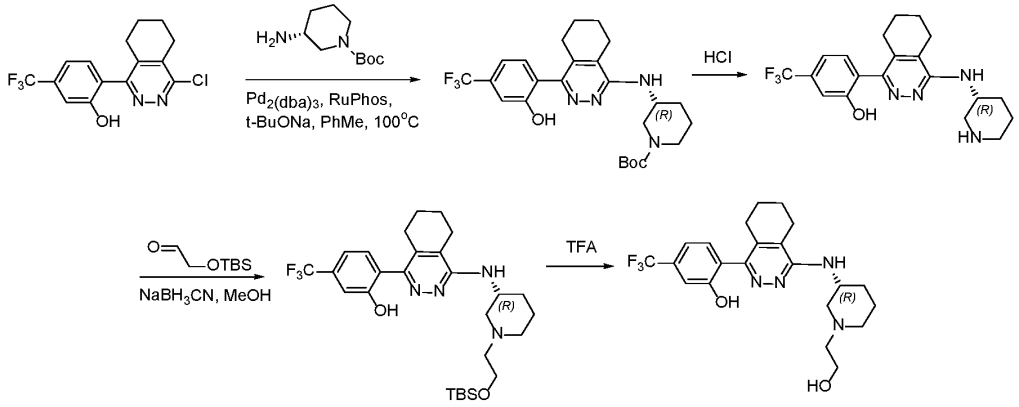
Step 5: 3-Cyclopropyl-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol and 3-cyclopropyl-2-[4-[[(3R)-1-methyl-3-piperidyl](14N)amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol

To a solution of 1-[2-cyclopropyl-6-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrido[3,4-d]pyridazin-4-amine (144 mg, 0.31 mmol) in dichloromethane (0.1 M, 3.1 ml) at 0 ºC was added BBr_3 (10 eq., 0.29 ml) dropwise. The resulting mixture was warmed to RT and stirred for 2 h, then quenched by careful addition of potassium carbonate and methanol in ice bath. The mixture was filtered to get rid of potassium carbonate and concentrated on vacuum. The residue was then purified on prep-HPLC with 5-50% ACN in water with 0.1% formic acid to provide 3-cyclopropyl-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (6 mg, 4.2% yield) as formic acid salt.

3-Cyclopropyl-2-[4-[[(3R)-1-methyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formic acid salt: MS *m/z* 444.3 $[M+H]^+$, ^1H NMR (400 MHz MeOD-d4) δ: 9.63 (s, 1H), 8.75 (d, J=5.5 Hz, 1H), 8.42 (s, 1H, formic acid), 7.20 (d, J=5.4 Hz, 1H), 6.96 (s, 1H), 6.77 (s, 1H), 4.50-4.66 (m, 1H), 3.30-3.41 (m, 1H), 2.99-3.17 (m, 1H), 2.79-2.97 (m, 1H), 2.53-2.61 (m, 1H), 2.49 (s, 3H), 2.00-2.16 (m, 1H), 1.84-1.97 (m, 1H), 1.58-1.82 (m, 2H), 1.39-1.53 (m, 1H), 0.71 (br d, J=7.5 Hz, 2H), 0.39-0.50 (m, 1H), 0.26-0.39 (m, 1H). NH and OH not observed.

Example 20

Preparation of Compounds I-11 and I-62



Step 1. tert-Butyl (3R)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydrophthalazin-1-yl]amino]piperidine-1-carboxylate

To a solution of tert-butyl (3R)-3-aminopiperidine-1-carboxylate (Intermediate 12, 366 mg, 1.83 mmol), and 2-(4-chloro-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol (600 mg, 1.83 mmol) in toluene (6 mL) was added sodium tert-butoxide (360 mg, 3.74 mmol), RuPhos (210 mg, 0.44 mmol) and tris-(dibenzylideneacetone)-dipalladium(0) (210 mg, 0.22 mmol). The reaction was stirred at 100 °C for 2 h under N_2. The reaction mixture was evaporated in vacuo. The crude residue was purified over silica gel using 20%-30% EA/PE to give tert-butyl (3R)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydrophthalazin-1-yl]amino]piperidine-1-carboxylate (280 mg, 31% Yield) as a yellow solid. MS *m/z* 493.2 $[M+H]^+$.

Step 2. (R)-2-(4-(Piperidin-3-ylamino)-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol

To a solution of tert-butyl (3R)-3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydrophthalazin-1-yl]amino]piperidine-1-carboxylate (330 mg, 0.67 mmol) was added hydrochloric acid in dioxane (10 mL, 40 mmol, 4 mol/L). The mixture was stirred at rt for 2.5 h, monitored by LCMS. The mixture was concentrated under vacuum to provide 2-[4-[[(3R)-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (270 mg, 100% Yield) as a pale powder. The crude product was applied to the next step without further purification. MS *m/z* 393.2 $[M+H]^+$.

The crude product can be purified by Prep-HPLC eluting with 5-50% ACN in water with 0.1% formic acid. ^{1}H NMR (MeOD-d4) δ:7.34 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.15 (s, 1H), 4.31 – 4.23 (m, 1H), 3.38 – 3.33 (m, 1H), 3.05 – 2.98 (m, 1H), 2.73 – 2.60 (m, 2H), 2.50 – 2.42 (m, 4H), 2.11 (s, 1H), 1.94 – 1.80 (m, 3H), 1.76 – 1.62 (m, 4H). NH and OH not observed.

Step 3. **2-[4-[[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol**

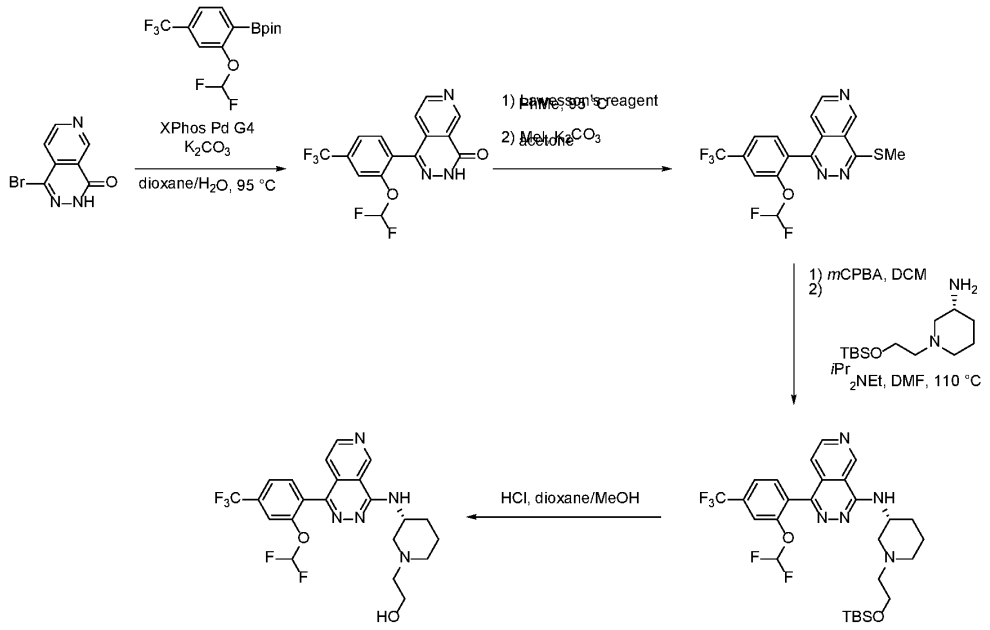
To a solution of 2-[4-[[(3R)-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (270 mg, 0.69 mmol) in methanol (5 mL) was added sodium acetate (60 mg, 0.73 mmol) and 2-[tert-butyl(dimethyl)silyl]oxyacetaldehyde (135 mg, 0.77 mmol), followed by sodium cyanoborohydride (130 mg, 2.069 mmol). The mixture was stirred at rt for 16 h, then concentrated under vacuum. The residue was purified by column chromatography (0−5% MeOH in DCM) to afford 2-[4-[[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (130 mg, 0.24 mmol, 34% Yield). 551.3 $[M+H]^+$.

Step 4. **2-[4-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol**

To a solution of 2-[4-[[(3R)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (4, 130 mg, 0.24 mmol) in DCM (2 mL) was added TFA (2 mL). This mixture was stirred at rt for 2 h then concentrated under vacuum. Sat.$NaHCO_3$ was added to adjust the pH = 7 and the mixture was extracted with EA. The organic layers was washed with water and brine, then dried and concentrated under vacuum to give a residue which was purified by column chromatography (0−5% MeOH in DCM) to afford 2-[4-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-5,6,7,8-tetrahydrophthalazin-1-yl]-5-(trifluoromethyl)phenol (40 mg, 39% Yield). MS *m/z* 437.0 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD-d4) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 4.48 – 4.38 (m, 1H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.18-3.15 (m, 1H), 2.83-2.80 (m, 1H), 2.74 – 2.61 (m, 2H), 2.49-2.44 (m, 6H), 2.00 – 1.81 (m, 4H), 1.80 – 1.58 (m, 4H), three exchangeable protons not observed.

Example 21

Preparation of Compound I-206



Step 1: 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-*d*]pyridazin-4-one

1-Bromo-*N*-pyridazin-4-one (Intermediate 1b, 0.500 g, 2.21 mmol), 2-[2-(difluoromethoxy)-4-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.860 g, 2.54 mmol), and XPhos Pd G4 (0.200 g, 0.221 mmol) were added to a vial and evacuated and refilled with Ar. The mixture was dissolved in dioxane (11.0 mL) and aqueous K_2CO_3 (2 M, 3.3 mL, 6.64 mmol). The mixture was sparged with Ar for 5 min then then heated at 95 °C for 2.5 h, diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 10 to 75%) gave a white solid (0.569 g, 72%). MS *m/z* 358.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1 H), 9.53 (s, 1H), 8.97 (d, *J* = 5.50 Hz, 1 H), 7.84 (s, 2H), 7.78 (d, 1 H), 7.37 (t, *J* = 72.54 Hz, 1 H), 7.28 (d, *J* = 5.38 Hz, 1 H).

Step 2. 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-d]pyridazine-4-thione

To 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-d]pyridazin-4-one

(0.393 g, 1.10 mmol) in PhMe (4.4 mL) was added Lawesson's reagent (0.298 g, 0.715 mmol). The mixture was heated at 95 °C for 3 h, then cooled to rt and filtered to give a pale-yellow solid (0.401 g, 98%). MS *m/z* 374.0 $[M+H]^+$.

Step 3: 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrido[3,4-d]pyridazine

To a solution of 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-3H-pyrido[3,4-d]pyridazine-4-thione (0.190 g, 0.509 mmol) in acetone (2 mL) was added MeI (0.033 mL, 0.534 mmol) and K_2CO_3 (0.091 g, 0.662 mmol). The mixture was stirred at rt for 3.5 h, then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 20-60%) gave a white solid (0.137 g, 70%). MS *m/z* 388.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 1.00 Hz, 1 H), 9.00 (d, *J* = 5.75 Hz, 1 H), 7.75 (s, 2 H), 7.67 (s, 1 H), 7.43 (dd, *J* = 5.75 Hz, 1.00 Hz, 1 H), 6.45 (t, *J* = 72.42 Hz, 1H), 2.95 (s, 3 H).

Step 4: *N*-[(3*R*)-1-[2-[tert-Butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine

A solution of 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrido[3,4-d]pyridazine (0.0750 g, 0.19747 mmol) in DCM (2 mL) was cooled to 0 °C. *m*-CPBA (0.058 g, 0.252 mmol) in DCM (1.5 mL) was added dropwise. After 30 min the reaction was warmed to rt and stirred for 2 h. The solution was diluted with DCM and washed with sat. $NaHCO_3$, water, brine, dried (MgSO4), filtered and concentrated to give a mixture of sulfoxide and sulfone. The crude material was dissolved in DMF (1.0 mL), to which was added (3*R*)-1-[2-[*t*-butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine (0.062 g, 0.24 mmol) and *i*Pr_2NEt (0.084 mL, 0.48 mmol). The mixture was stirred at 110 °C for 16 h, then cooled to rt and diluted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 20%) gave a yellow solid. MS *m/z* 598.7 $[M+H]^+$.

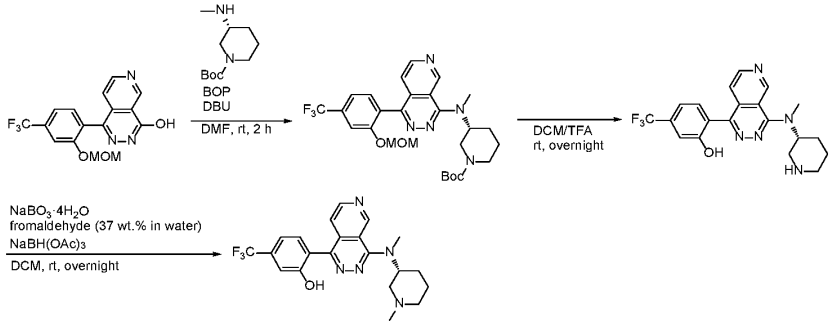
Step 5: 2-[(3*R*)-3-[[1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl]amino]-1-piperidyl]ethanol formic acid salt

To a solution of *N*-[(3*R*)-1-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-3-piperidyl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine in MeOH (0.5mL) was added 4M HCl/dioxane (1.0 mL). The mixture was stirred at rt for 3 h, then diluted with

DCM/iPrOH (9:1) and washed with saturated $NaHCO_3$, water, and brine. The organics were dried (Na_2SO_4), filtered, and concentrated to give a brown oil. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.011 g, 10%). MS *m/z* 484.5$[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H, formic acid), 7.87 – 7.70 (m, 4H), 7.35 (t, J = 73.29 Hz, 1 H), 7.27 (d, J = 5.88 Hz, 1 H), 4.55 – 4.41 (m, 2H), 3.53 (t, J = 5.6 Hz, 2H), 3.22 – 3.12 (m, 1H), 2.89 – 2.77 (m, 1H), 2.48 – 2.43 (m, 2H), 2.20 – 1.95 (m, 3H), 1.81 – 1.72 (m, 1H), 1.68 – 1.44 (m, 2H).

Example 22

Preparation of Compounds I-292 and I-297



Step 1. tert-Butyl (R)-3-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)(methyl)amino)piperidine-1-carboxylate

To a solution of 1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-*d*]pyridazin-4-ol (Intermediate 14a, 400 mg, 1.14 mmol, 1.0 eq.), BOP (623 mg, 1.37 mmol, 1.2 eq.),1,8-diazabicyclo[5.4.0]undec-7-ene (0.43 mL, 2.85 mmol, 2.5 eq.) in DMF (0.2 M) was added *tert*-butyl (3*R*)-3-(methylamino)piperidine-1-carboxylate (1.46 g, 6.83 mmol, 3.0 eq.) The mixture was allowed to stir at room temperature for 2 hours. Upon completion, the mixture was diluted with EtOAc, washed with water and brine. The organic phase was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-50% EtOAc in DCM to afford *tert*-butyl (*R*)-3-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-*d*]pyridazin-4-yl)(methyl)amino)piperidine-1-carboxylate (623 mg). The impure isolated material was used in

next step without further purification. MS *m/z* 548.3 $[M+H]^+$.

Step 2. (*R*)-2-(4-(Methyl(piperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

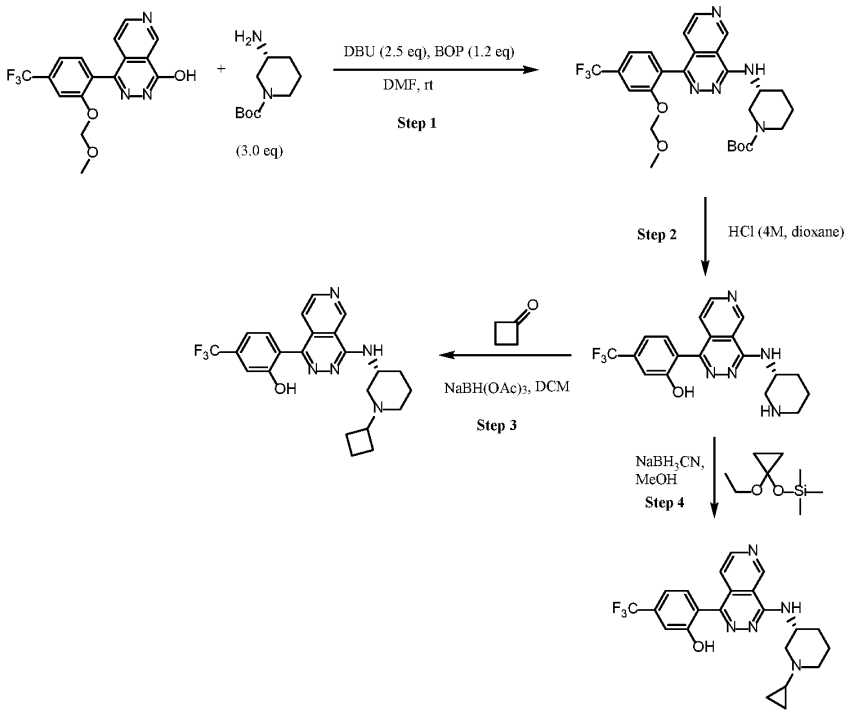
The crude from step 1 was dissolved in 5 ml DCM and 5ml TFA at rt. The reaction was allowed to stir overnight. Upon completion, the solvent was removed under reduced pressure. The crude residue was purified by reverse phase column (MeCN/water with 0.1% formic acid) to afford (*R*)-2-(4-(methyl(piperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol (131.9 mg, 29% over two steps) as a pale yellow solid. MS *m/z* 404.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.68 (s, 1H), 8.94 (s, 1H), 7.73 – 7.52 (m, 2H), 7.45 – 7.22 (m, 2H), 4.71 – 4.61 (m, 1H), 3.94 – 3.72 (m, 1H), 3.51 – 3.35 (m, 5H), 3.09 – 2.98 (m, 1H), 2.32 – 2.11 (m, 3H), 2.01 – 1.81 (m, 1H), 1 NH and 1 OH not observed.

Step 3. (*R*)-2-(4-(Methyl(1-methylpiperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol

To a mixture of (*R*)-2-(4-(methyl(piperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol (45 mg, 0.11 mmol, 1.0 eq.) and sodium perborate tetrahydrate (51.4 mg, 0.33 mmol, 3 eq.) in DCM (0.1 M) was added formaldehyde (37 wt.% in water, 0.03 mL, 0.33 mmol, 3 eq.) followed by sodium triacetoxyborohydride (71 mg, 0.33 mmol, 3 eq.). The mixture was stirred at room temperature overnight. Upon completion, the mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried over sodium sulphate, filtered, and concentrated under reduced pressure. The crude residue was purified by reverse phase column (MeCN/water with 0.1% formic acid) to give (*R*)-2-(4-(methyl(1-methylpiperidin-3-yl)amino)pyrido[3,4-*d*]pyridazin-1-yl)-5-(trifluoromethyl)phenol (3.6 mg, 7.7%) as a yellow solid. MS *m/z* 418.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.61 (s, 1H), 8.91 (s, 1H), 8.01 – 7.50 (m, 2H), 7.44 – 7.09 (m, 2H), 4.62 – 4.21 (m, 1H), 3.55 – 3.25 (m, 4H), 3.15 – 2.97 (m, 1H), 2.85 – 2.62 (m, 1H), 2.50 (s, 3H), 2.38 – 2.21 (m, 1H), 2.21 – 2.09 (m, 1H), 2.04 – 1.87 (m, 2H), 1.83 – 1.68 (m, 1H), 1 OH not observed.

Example 23

Preparation of Compounds I-219 and I-215



Step 1. tert-Butyl (3R)-3-[[1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-1-carboxylate

To a mixture of 1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-ol (Intermediate 14b, 50 mg, 0.14 mmol) and tert-butyl (3R)-3-aminopiperidine-1-carboxylate (86 mg, 3.0 eq.) in DBU (57 mg, 2.5 eq.) and DMF (0.7 mL) was added BOP (72 mg, 1.1 eq.). The reaction was stirred at rt overnight. The reaction was quenched with EtOAc and water. The organic phase was washed with H_2O followed by brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexane provide the desired product which was further purified on prep-HPLC with 10-100% ACN in water with 0.1% formic acid to provide tert-butyl (3R)-3-[[1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-1-carboxylate (43 mg, 57 % yield). MS *m/z* 534.2 $[M+H]^+$.

Step 2. 2-[4-[[(3R)-3-Piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol hydrochloride

tert-Butyl (3R)-3-[[1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-1-carboxylate (100 mg, 0.19 mmol) was stirred in a solution of HCl (4 M in dioxane, 1 mL) at room temperature for 1 h. The organic volatiles were removed. The residue was triturated with diethyl ether and filtered to afford 2-[4-[[(3R)-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (80 mg, 92 % yield) as hydrochloride salt. MS *m/z* 390.5 $[M+H]^+$.

Step 3. 2-[4-[[(3R)-1-Cyclobutyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (I-219)

A mixture of 2-[4-[[(3R)-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol hydrochloride (35 mg, 0.076 mmol) and sodium perborate tetrahydrate (31 mg, 5.0 eq.) in DIPEA (20 mg, 2.0 eq.) and DCM (0.75 mL) was stirred for 15 mins, followed by addition of cyclobutanone (7.04 mg, 1.3 eq.) and $NaBH(OAc)_3$ (49 mg, 3.0 eq.). After 15 mins, the reaction was quenched by dilution with DCM and aq. $NaHCO_3$ (sat.). The organic phase was washed with H_2O followed by brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-20% MeOH (with NH_4OH as modifier) in DCM to provide 2-[4-[[(3R)-1-cyclobutyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (16 mg, 48% yield). MS *m/z* 444.5 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 9.72 (s, 1H), 8.87 (d, J=5.8 Hz, 1H), 7.59 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.8 Hz, 1H), 7.26-7.36 (m, 2H), 4.61-4.72 (m, 1H), 2.81-3.17 (m, 3H), 2.24-2.43 (m, 2H), 2.14-2.24 (m, 3H), 1.93-2.12 (m, 3H), 1.71-1.89 (m, 4H). NH and OH not observed.

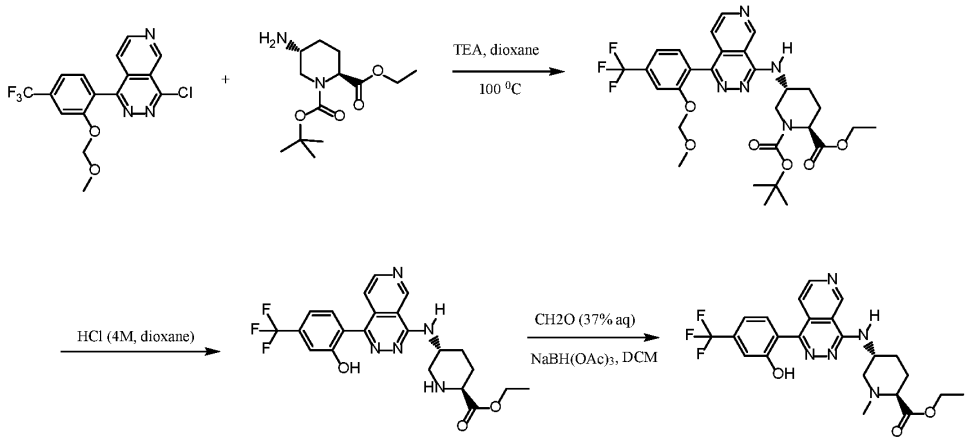
Step 4. (R)-2-(4-((1-Cyclobutylpiperidin-3-yl)amino)pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol (I-215)

To a mixture of 2-[4-[[(3R)-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol hydrochloride (product in step 2, 35 mg, 0.076 mmol) and DIPEA (10 mg, 1.0 eq.) in MeOH (1.5 mL) was added **(1-ethoxycyclopropoxy)trimethylsilane** (54 mg, .0 eq.) and sodium cyanoborohydride (10 mg, 2.0 eq.). The reaction was stirred at rt for 2 days. The reaction was quenched by dilution with DCM and aq. $NaHCO_3$ (sat.). The organic phase was washed with H_2O followed by brine. The organic phase was dried over Na_2SO_4, filtered and

concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-20% MeOH (with NH_4OH as modifier) in DCM provide 2-[4-[[(3R)-1-cyclopropyl-3-piperidyl]amino]pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol (15 mg, 46 % yield). MS *m/z* 430.5 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 9.56-9.60 (m, 1H), 8.74 (d, J=5.8 Hz, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.37 (dd, J=5.7, 0.8 Hz, 1H), 7.13-7.24 (m, 2H), 4.42-4.54 (m, 1H), 3.23-3.30 (m, 1H), 2.79-2.89 (m, 1H), 2.30-2.43 (m, 2H), 1.97-2.08 (m, 1H), 1.69-1.78 (m, 1H), 1.52-1.69 (m, 3H), 0.36-0.48 (m, 4H). NH and OH not observed.

Example 24

Preparation of Compounds I-266 and I-318



Step 1. 1-(tert-Butyl) 2-ethyl (2S,5R)-5-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)piperidine-1,2-dicarboxylate

A mixture of 4-chloro-1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazine (Intermediate 14b, 63 mg, 0.17 mmol) and 1-(tert-butyl) 2-ethyl (2S,5R)-5-aminopiperidine-1,2-dicarboxylate (62 mg, 1.30 eq.) in triethylamine (19 mg, 1.10 eq.) and dioxane (0.7 mL) was heated at 100°C for 24 hr. After cooling, the reaction mixture was concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in DCM to provide 1-(tert-butyl) 2-ethyl (2S,5R)-5-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)piperidine-1,2-dicarboxylate (85 mg, 83 % yield). MS *m/z* 606.6 $[M+H]^+$.

Step 2. Ethyl (2S,5R)-5-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)piperidine-2-carboxylate hydrochloride

1-(tert-Butyl) 2-ethyl (2S,5R)-5-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)piperidine-1,2-dicarboxylate (85 mg, 0.14 mmol) was stirred in a solution of HCl (4 M in dioxane, 1 mL) at room temperature for 1 h. The organic volatiles were removed. The residue was triturated with diethyl ether and filtered to affordethyl (2S,5R)-5-[[1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-2-carboxylate (65 mg, 93 % yield). as hydrochloride salt. MS *m/z* 462.5 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 9.98-10.05 (m, 1H), 9.15-9.20 (m, 1H), 7.77-7.82 (m, 1H), 7.70 (br d, J=8.1 Hz, 1H), 7.45 (d, J=8.4 Hz, 1H), 7.38 (s, 1H), 4.58-4.70 (m, 1H), 4.33-4.42 (m, 2H), 4.18-4.30 (m, 1H), 3.89-3.97 (m, 1H), 3.20-3.29 (m, 1H), 2.55-2.65 (m, 1H), 2.43-2.53 (m, 1H), 1.97-2.15 (m, 2H), 1.35-1.42 (m, 3H). NH and OH not observed.

Step 3. Ethyl (2S,5R)-5-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)pyrido[3,4-d]pyridazin-4-yl)amino)-1-methylpiperidine-2-carboxylate

To a mixture of ethyl (2S,5R)-5-[[1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl]amino]piperidine-2-carboxylate hydrochloride (20 mg, 0.040 mmol) and sodium perborate tetrahydrate (16 mg, 5.0 eq.) in DIPEA (5.3 mg, 1.0 eq.) and DCM (0.40 mL) was stirred for 15 mins, followed by addition of CH_2O (aq. 37 mass%, 6.5 mg, 2.0 eq.) and $NaBH(OAc)_3$ (26 mg, 3.0 eq.). After 15 mins, the reaction was quenched by dilution with DCM and $NaHCO_3$ (sat.). The organic phase was washed with H_2O followed by brine. The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-20% MeOH (with NH_4OH as modifier) in DCM to provide ethyl (2S,5R)-5-[[1-[2-hydroxy-4-(trifluoromethyl)phenyl]-pyrido[3,4-d]pyridazin-4-yl]amino]-1-methyl-piperidine-2-carboxylate (10 mg, 52 % yield). MS *m/z* 476.5 $[M+H]^+$. ^1H NMR (CD_3OD) δ: 9.69 (s, 1H), 8.86 (d, J=5.6 Hz, 1H), 7.59 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.5 Hz, 1H), 7.33 (br d, J=7.9 Hz, 1H), 7.28 (s, 1H), 4.60-4.72 (m, 1H), 4.25 (q, J=7.2 Hz, 2H), 3.40-3.51 (m, 1H), 2.85 (br d, J=9.8 Hz, 1H), 2.30-2.38 (m, 4H), 2.22-2.28 (m, 1H), 2.04-2.16(m, 1H), 1.78-1.93 (m, 1H), 1.54-1.69 (m, 1H), 1.29-1.35 (t, J=7.2 Hz, 3H). NH and OH not observed.

The compounds below were prepared according to the procedure of Example 24 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-19	MS *m/z* 421.2 $[M+H]^+$

Compound	Spectral Data
	^{1}H NMR (400 MHz, CD_3OD) δ 7.37 – 7.32 (m, 1H), 7.20 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.17 – 7.14 (m, 1H), 4.48 – 4.37 (m, 1H), 3.23 – 3.09 (m, 1H), 2.88 – 2.71 (m, 1H), 2.64 – 2.51 (m, 2H), 2.49 – 2.42 (m, 4H), 2.41 – 2.24 (m, 2H), 2.06 – 1.95 (m, 1H), 1.93 – 1.80 (m, 3H), 1.78 – 1.67 (m, 3H), 1.65 – 1.54 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H), NH and OH not observed.
I-26	MS *m/z* 393.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.13 (dd, J = 8.0, 1.6 Hz, 1H), 5.87 (s , 1H), 5.15-5.05 (m, 1H), 3.63 – 3.53 (m, 1H), 3.45 – 3.35 (m, 1H), 3.00 – 2.91 (m, 1H), 2.79 – 2.60 (m, 7H), 2.65 – 2.54 (m, 2H), 2.20 – 2.10 (m, 2H), 1.98 – 1.89 (m, 2H), 1.73 – 1.65 (m, 2H).
I-34	MS *m/z* 435.0 $[M+H]^+$; ^{1}H NMR (400 MHz, MeOD-d4) δ 7.34 (d, J = 7.8 Hz, 1H), 7.21 – 7.17 (dd, J = 7.8, 1.2 Hz, 1H), 7.15 (d, J = 1.2 Hz, 1H), 4.46 – 4.36 (m, 1H), 3.20 – 3.10 (m, 1H), 2.91 – 2.82 (m, 1H), 2.80 – 2.72 (m, 1H), 2.52 – 2.32 (m, 6H), 2.00 – 1.78 (m, 4H), 1.71 m, 3H), 1.63 – 1.52 (m, 1H), 1.11 (d, J = 6.6 Hz, 6H), NH and OH not observed.
I-115	MS *m/z* 417.3 $[M+H]^+$; ^{1}H NMR (CHLOROFORM-d) δ: 8.24 (d, J=8.0 Hz, 1H), 7.82-7.95 (m, 3H), 7.72 (d, J=8.0 Hz, 1H), 7.42 (s, 1H), 7.23 (d, J=8.4 Hz, 1H), 6.67 (br d, J=3.8 Hz, 1H), 3.77 (br t, J=5.8 Hz, 2H), 2.78 (t, J=5.8 Hz, 2H), 2.54 (br s, 4H), 1.67 (quin, J=5.5 Hz, 4H), 1.25 (s, 2H), 0.88 (br t, J=6.5 Hz, 1H).
I-116	MS *m/z* 390.1 $[M+H]^+$; ^{1}H NMR (DMSO-d6) δ: 10.66 (br s, 1H), 8.94-8.99 (m, 2H), 7.96 (dd, J=5.8, 0.8 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.35-7.38 (m, 1H), 7.33 (s, 1H), 3.49-3.61 (m, 4H), 2.58-2.71 (m, 4H), 2.31 (s, 3H).
I-147	MS *m/z* 433.0 $[M+H]^+$; ^{1}H NMR (DMSO-d6) δ: 10.26-10.52 (br s, 1H), 8.28 (d, J=8.3 Hz, 1H), 7.87 (t, J=7.2 Hz, 1H), 7.78 (t, J=7.3 Hz, 1H), 7.49-7.57 (m, 2H), 7.45 (d, J=7.8 Hz, 1H), 7.25-7.33 (m, 2H), 3.75-3.84 (m, 1H), 3.66-3.75 (m, 2H), 3.61 (br dd, J=11.0, 3.0 Hz, 1H), 3.49-3.55 (m, 1H), 3.11 (br dd, J=10.9, 8.9 Hz, 1H), 2.98-3.06 (m, 1H), 2.85 (br d, J=11.8 Hz, 1H), 2.55-2.68 (m, 1H), 2.44-2.48 (m, 1H), 0.98 (d, J=6.3 Hz, 3H).
I-148	MS *m/z* 433.0 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.20 (d, J=8.3 Hz, 1H), 7.89 (t, J=7.3 Hz, 1H), 7.81 (t, J=7.6 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.53 (d, J=7.8 Hz, 1H), 7.30 (d, J=7.8 Hz, 1H), 7.25 (s, 1H), 3.65-3.93 (m, 5H), 3.20-3.29 (m, 2H), 3.04 (dt, J=12.0, 2.8 Hz, 1H), 2.74 (ddd, J=12.8, 7.0, 5.3 Hz, 1H), 2.63-2.70 (m, 1H), 2.59 (ddd, J=12.0, 10.0, 3.3 Hz, 1H), 1.08 (d, J=6.5 Hz, 3H). NH and OH not observed
I-149	MS *m/z* 418.2 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.23 (d, J=8.0 Hz, 1H), 7.89 (ddd, J=8.3, 7.2, 1.1 Hz, 1H), 7.81 (td, J=7.7, 1.3 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.30 (d, J=7.6 Hz, 1H), 7.25 (s, 1H), 3.86 (t, J=6.4 Hz, 2H), 3.16-3.24 (m, 4H), 2.83-2.92 (m, 6H). NH and OH not observed
I-150	MS *m/z* 375.0 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 – 8.22 (m, 1H), 7.97 – 7.80 (m, 2H), 7.67 – 7.62 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.31 – 7.22 (m, 2H), 4.82 – 4.71 (m, 1H), 4.17 – 4.06 (m, 1H), 4.04 – 3.86 (m, 3H), 2.67 – 2.46 (m, 2H), OH and NHs not observed.
I-152	MS *m/z* 418.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.8 (bs, 1H), 8.98 (s, 2H), 7.95 (d, J= 4.0 Hz, 1H), 7.65 (d, J= 4.0 Hz, 1H), 7.38-7.36 (m, 2H),

Compound	Spectral Data
	4.16-4.15 (m, 1H), 3.90-3.87 (m, 1H), 3.08-3.03 (m, 3H), 2.50-2.47 (m, 6H, overlapped with d-DMSO peak), 2.12-2.10 (m, 1H), 1.99-1.97 (m, 1H), 1.93-1.91 (m, 1H), 1.83-1.80 (m, 1H).
I-153	MS *m/z* 390.0 $[M+H]^+$; ^1H NMR (DMSO-d6) δ: 8.97 (d, J=5.8 Hz, 1H), 8.89 (s, 1H), 7.97 (d, J=5.5 Hz, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.50-7.58 (m, 2H), 3.80 (s, 3H), 3.44-3.47 (m, 1H), 3.34 (br s, 4H), 3.00 (br s, 4H).
I-161	MS *m/z* 432.0 $[M+H]^+$; ^1H NMR (CHLOROFORM-d) δ: 8.25 (d, J=8.0 Hz, 1H), 7.79-8.01 (m, 3H), 7.72 (d, J=8.0 Hz, 1H), 7.43 (s, 1H), 7.24 (br d, J=8.3 Hz, 1H), 6.34-6.58 (m, 1H), 3.81 (br t, J=5.3 Hz, 2H), 2.84 (br t, J=5.8 Hz, 2H), 2.44-2.71 (m, 6H), 2.29-2.40 (m, 3H).
I-162	MS *m/z* 432.0 $[M+H]^+$; ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.98 (s, 1H), 8.90 (d, J= 4.0 Hz, 1H), 7.78 (d, J= 4.0 Hz, 1H), 7.68 (d, J= 8.0 Hz, 1H), 7.44 (d, J= 4.0 Hz, 1H), 7.27 (d, J= 8.0 Hz, 1H), 4.25 (d, J= 12.0 Hz, 1H), 4.00 (d, J= 12.0 Hz, 1H), 3.78 (s, 3H), 3.06-3.03 (m, 2H), 2.75-2.70 (m, 1H), 2.40 (s, 6H), 2.19-2.16 (m, 1H), 1.99-1.97 (m, 1H), 1.89-1.85 (m, 1H), 1.59-1.55 (m, 1H).
I-174	MS *m/z* 401.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.44 (s, 1H), 9.73 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 8.39 (t, J = 5.4 Hz, 1H), 7.72 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.48 (s, 1H), 7.35 – 7.25 (m, 3H), 4.68 (d, J = 5.1 Hz, 2H), 3.80 (s, 3H)
I-180	MS *m/z* 387.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.48 (s, 1H), 10.00 (s, 1H), 9.92 (s, 1H), 8.90 (d, J = 5.6 Hz, 1H), 8.35 (s, 1H), 7.75 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38 – 7.30 (m, 3H), 3.89 (s, 3H)
I-199	MS *m/z* 430.8 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.80 (d, J = 1.0 Hz, 1H), 8.83 (d, J = 5.7 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.33 (dd, J = 5.7, 1.0 Hz, 1H), 4.49 (s, 1H), 3.81 (d, J = 1.9 Hz, 1H), 3.80 (s, 3H), 3.50 (ddd, J = 14.0, 9.5, 2.4 Hz, 1H), 3.17 – 3.03 (m, 1H), 2.99 – 2.84 (m, 3H), 2.34 (d, J = 4.1 Hz, 1H), 2.05 (tdd, J = 14.7, 5.5, 2.9 Hz, 1H), 1.93 – 1.77 (m, 2H), 1.67 – 1.53 (m, 1H). NH and OH not observed.
I-203	MS *m/z* 417.2 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.44 (d, J = 8.3 Hz, 1H), 7.90 - 7.76 (m, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.28 - 7.25 (m, 1H), 4.13 - 3.94 (m, 3H), 3.77 (dd, J = 8.1, 10.4 Hz, 1H), 2.68 - 2.46 (m, 3H), 2.34 (s, 6H), 2.32 - 2.24 (m, 1H), 1.83 (qd, J = 8.7, 11.9 Hz, 1H); OH wasn't observed
I-212	MS *m/z* 430.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.93 (d, J = 1.0 Hz, 1H), 9.10 (d, J = 5.6 Hz, 1H), 7.72 – 7.56 (m, 2H), 7.37 (dd, J = 8.3, 1.7 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 4.58 (tt, J = 11.3, 4.5 Hz, 1H), 3.64 (d, J = 13.1 Hz, 2H), 3.09 (s, 3H), 2.72 (t, J = 13.0 Hz, 1H), 2.46 (d, J = 14.2 Hz, 1H), 2.35 (dd, J = 17.1, 11.3 Hz, 1H), 1.79 (s, 1H), 1.39 – 1.25 (m, 2H), 1.22 – 1.10 (m, 1H), 1.01 (d, J = 9.5 Hz, 1H). NH and OH not observed.
I-213	MS *m/z* 444.7 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.62 (dd, J = 7.9, 1.0 Hz, 1H), 8.82 (dd, J = 11.8, 5.7 Hz, 1H), 7.61 (dd, J = 8.1, 1.7 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.32 (ddd, J = 11.7, 5.7, 1.0 Hz, 1H), 4.40 (t, J = 6.4 Hz, 1H), 3.80 (d, J = 1.1 Hz, 3H), 3.30 (s, 1H), 3.24 (d, J = 4.3 Hz, 1H), 2.36 (d, J = 12.1

Compound	Spectral Data
	Hz, 3H), 2.30 (td, J = 7.3, 3.2 Hz, 1H), 2.23 – 2.05 (m, 5H), 1.96 – 1.77 (m, 2H). NH and OH not observed.
I-224	MS *m/z* 404.8 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.77 (br s, 1H), 8.89 (d, J = 5.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 5.8 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.32 - 7.28 (m, 1H), 4.70 - 4.52 (m, 1H), 3.75 - 3.58 (m, 2H), 2.96 (s, 3H), 2.52 (br s, 2H), 2.13 (br s, 2H); 2CH was overlapped with solvent peak. OH and NH wasn't observed.
I-230	MS *m/z* 406.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.00 – 8.93 (m, 2H), 8.50 (s, 1H), 8.19 (d, J = 5.8 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.29 (s, 1H), 4.85 – 4.78 (m, 1H), 4.20 (dd, J = 12.8, 5.1 Hz, 1H), 4.10 – 3.96 (m, 3H), 3.55 (d, J = 5.0 Hz, 2H), 3.30 – 3.25 (m, 2H).
I-233	MS *m/z* 404.8 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.57 (s, 1H), 8.91 (d, J = 5.6 Hz, 1H), 7.64 - 7.56 (m, 2H), 7.40 - 7.34 (m, 1H), 7.34 - 7.28 (m, 1H), 4.39 (br d, J = 12.1 Hz, 1H), 4.08 (br d, J = 13.0 Hz, 1H), 3.43-3.37 (m, 3H), 2.74 (s, 6H), 2.30 (br d, J = 10.1 Hz, 1H), 2.14 - 1.91 (m, 2H), 1.91 - 1.72 (m, 1H); OH wasn't observed
I-238	MS *m/z* 483.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.98 (d, J = 5.6 Hz, 1H), 8.81 (s, 1H), 8.35 (d, J = 5.8 Hz, 1H), 8.16 (s, 1H, formic acid), 7.89 – 7.80 (m, 2H), 7.74 (s, 1H), 7.57 (s, 1 H), 7.38 (t, J = 73.5 Hz, 1H), 4.54 – 4.37 (m, 2H), 3.53 (t, J = 6.2 Hz, 2H), 3.20 – 3.12 (m, 1H), 2.88 – 2.79 (m, 1H), 2.48 – 2.44 (m, 2H), 2.19 – 1.95 (m, 3H), 1.83 – 1.69 (m, 1H), 1.68 – 1.41 (m, 2H)
I-243	MS *m/z* 416.3 $[M-H]^-$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.67 (s, 1H), 8.85 (d, J = 5.8 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 5.6 Hz, 1H), 7.33 - 7.23 (m, 2H), 4.11 (dd, J = 4.0, 13.9 Hz, 1H), 3.72 (dd, J = 6.1, 13.9 Hz, 1H), 3.08 - 2.95 (m, 1H), 2.67 - 2.58 (m, 1H), 2.56 (s, 3H), 2.35 (dt, J = 4.4, 11.2 Hz, 1H), 1.94 (br dd, J = 3.0, 13.4 Hz, 1H), 1.88 - 1.79 (m, 1H), 1.78 - 1.51 (m, 3H), 1.48 - 1.36 (m, 1H); NH and OH wasn't observed.
I-251	MS *m/z* 418.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.69 (s, 1H), 8.88 (d, J = 5.7 Hz, 1H), 8.54 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.38 (d, J = 5.7 Hz, 1H), 4.62 (s, 1H), 3.64 (dd, J = 13.8, 3.9 Hz, 1H), 3.48 – 3.34 (m, 2H), 3.29 – 3.18 (m, 1H), 2.38 – 2.26 (m, 1H), 2.19 – 1.89 (m, 4H), 1.85 – 1.68 (m, 1H).
I-252	MS *m/z* 406.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.69 (s, 1H), 8.90 (d, J = 5.7 Hz, 1H), 8.47 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 5.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 4.82-4.71 (m, 1H), 4.22 (dd, J = 12.7, 5.1 Hz, 1H), 4.12 – 3.99 (m, 3H), 3.61 (d, J = 5.0 Hz, 2H), 3.42-3.33 (m, 1H), 3.28-3.18 (m, 1H).
I-253	MS *m/z* 404.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.70 (s, 1H), 8.87 (d, J = 5.7 Hz, 1H), 8.54 (brs, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 4.65 – 4.53 (m, 1H), 3.53 – 3.35 (m, 3H), 3.30 – 3.21 (m, 1H), 2.57 – 2.32 (m, 2H), 2.23 – 2.10 (m, 2H), 2.04 – 1.90 (m, 2H).

Compound	Spectral Data
I-257	MS *m/z* 508.2 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 9.82 (s, 1H), 9.01 (s, 1H), 7.62 (d, J = 7.3 Hz, 2H), 7.44 – 7.24 (m, 2H), 6.07 – 5.73 (m, 1H), 5.49 (d, J = 7.5 Hz, 1H), 4.67 (s, 1H), 3.95 (s, 1H), 3.80 – 3.46 (m, 2H), 2.97 – 2.66 (m, 2H), 2.60 (d, J = 16.9 Hz, 2H), 2.48 – 2.12 (m, 3H), 2.03 (s, 5H), NH and OH not observed.
I-260	MS *m/z* 420.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.99 – 8.89 (m, 2H), 8.19 (d, J = 5.7 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.28 (s, 1H), 4.86 – 4.78 (m, 1H), 4.15 (dd, J = 12.6, 4.8 Hz, 1H), 3.98 (dd, J = 12.7, 5.4 Hz, 1H), 3.93 – 3.78 (m, 2H), 3.12 – 2.98 (m, 2H), 2.91 – 2.76 (m, 2H), 2.52 (s, 3H).
I-261	MS *m/z* 404.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.68 (s, 1H), 8.90 (d, J = 5.7 Hz, 1H), 8.53 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 5.7 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.28 (s, 1H), 4.68 – 4.55 (m, 1H), 3.65 (dd, J = 13.8, 4.0 Hz, 1H), 3.47 – 3.34 (m, 2H), 3.28 – 3.18 (m, 1H), 2.44 – 2.24 (m, 1H), 2.20 – 1.91 (m, 4H), 1.84 – 1.71 (m, 1H).
I-262	MS *m/z* 420.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.68 (s, 1H), 8.88 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.27 (s, 1H), 4.19 (dd, J = 12.7, 5.1 Hz, 1H), 4.97-4.87 (m, 1H), 4.01 (dd, J = 12.6, 5.9 Hz, 1H), 3.96 – 3.82 (m, 2H), 3.28 – 3.15 (m, 2H), 3.10 – 2.90 (m, 2H), 2.64 (s, 3H).
I-263	MS *m/z* 418.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.69 (s, 1H), 8.86 (d, J = 5.7 Hz, 1H), 8.56 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 4.72 – 4.56 (m, 1H), 3.41-3.34 (m, 1H), 3.23 (s, 3H), 2.80 (s, 3H), 2.48 – 2.31 (m, 2H), 2.24 – 1.92 (m, 4H).
I-264	MS *m/z* 433.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.64 (s, 1H), 8.88 (d, J = 5.7 Hz, 1H), 8.52 (s, 1H, formic acid), 7.58 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 5.7 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 4.83 – 4.74 (m, 1H), 3.22 (dd, J = 13.4, 4.7 Hz, 2H), 3.15 (dd, J = 13.5, 6.1 Hz, 2H), 3.06 – 2.87 (m, 4H), 2.58 (s, 6H).
I-269	MS *m/z* 404.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.48 (br s, 1 H), 9.77 (s, 1 H), 8.84 (d, J = 5.63 Hz, 1 H), 8.19 (s, 1 H, formic acid), 7.76 (d, J = 7.63 Hz, 1 H), 7.55 (d, J = 7.88 Hz, 1 H), 7.34 - 7.25 (m, 3 H), 4.78 - 4.66 (m, 1 H), 4.40 - 4.27 (m, 1 H), 3.62 - 3.49 (m, 1 H), 2.29 (d, J = 11.63 Hz, 1 H), 2.11 – 1.96 (m, 1 H), 1.88 (d, J = 11.01 Hz, 1 H), 1.84 - 1.72 (m, 1 H), 1.44 - 1.23 (m, 3 H), 1.21 - 1.06 (m, 1 H)
I-270	MS *m/z* 404.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.49 (br s, 1 H), 9.79 (s, 1 H), 8.83 (d, J = 5.50 Hz, 1 H), 8.21 (s, 1 H, formic acid), 7.63 – 7.51 (m, 2 H), 7.37 – 7.22 (m, 3 H), 4.81 - 4.65 (m, 1 H), 4.56 - 4.44 (m, 1 H), 4.13 – 4.02 (m, 1 H), 2.10 – 1.88 (m, 2 H), 1.86 - 1.67 (m, 2 H), 1.66 - 1.23 (m, 2 H), 1.51 - 1.34 (m, 2 H)
I-271	MS *m/z* 446.8 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.72 (s, 1H), 8.86 (d, J = 5.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.30 - 7.26 (m, 1H), 4.74 (s, 5H), 3.59 (quin, J = 6.4 Hz, 1H), 3.19 - 3.05 (m, 1H), 2.68 (s, 1H), 2.23 - 2.03 (m, 3H), 1.97 - 1.86 (m, 1H), 1.85 - 1.62 (m, 2H); OH and NH wasn't observed

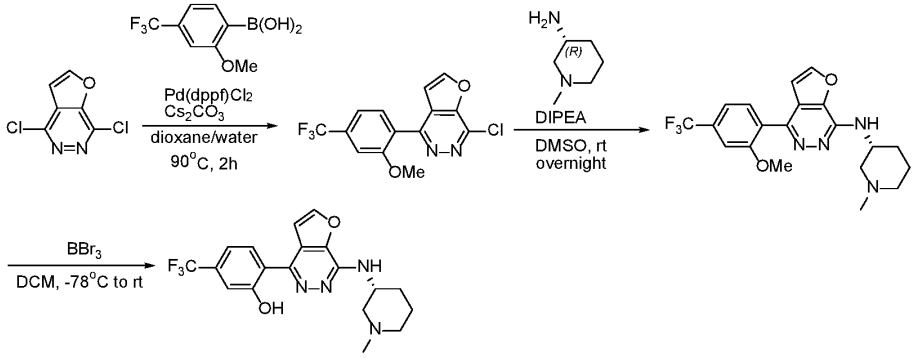
Compound	Spectral Data
I-272	MS *m/z* 372.1 [M-H]-; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.73 (s, 1H), 8.84 (d, J = 5.6 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 7.12 - 7.04 (m, 1H), 4.72 - 4.56 (m, 1H), 3.24 - 3.06 (m, 1H), 2.81 - 2.65 (m, 1H), 2.38 (s, 5H), 2.07 (s, 4H), 2.04 - 1.95 (m, 1H), 1.95 - 1.85 (m, 1H), 1.85 - 1.60 (m, 2H), 1.09 - 1.00 (m, 2H), 0.82 - 0.74 (m, 2H); NH wasn't observed
I-275	MS *m/z* 406.3 [M+H]$^+$; ^{1}H NMR (400 MHz, MeOD) δ 9.71 (s, 1H), 8.90 (s, 1H), 8.55 (s, 1H, formic acid proton), 7.89 – 7.40 (m, 2H), 7.40 – 7.14 (m, 2H), 3.88 (s, 2H), 2.64 (s, 6H), 1.35 (s, 6H). 1 OH and 1 NH not observed.
I-277	MS *m/z* 454.3 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.94 (s, 1H), 9.11 (s, 1H), 7.65 (dd, J = 12.5, 6.6 Hz, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.33 (s, 1H), 6.69 – 5.72 (m, 1H), 4.77 – 4.37 (m, 1H), 3.80 (d, J = 11.5 Hz, 1H), 3.75 – 3.40 (m, 3H), 3.07 (q, J = 12.6 Hz, 2H), 2.29 (d, J = 12.4 Hz, 1H), 2.24 – 2.10 (m, 1H), 2.06 – 1.78 (m, 2H), NH and OH not observed.
I-281	MS *m/z* 458.2 [M-H]-; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.71 (s, 1H), 8.86 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.33 (br d, J = 8.0 Hz, 1H), 7.30 - 7.26 (m, 1H), 4.63 (br t, J = 8.9 Hz, 1H), 4.02 - 3.84 (m, 2H), 3.83 - 3.69 (m, 2H), 3.25 - 3.09 (m, 2H), 2.89 (br d, J = 10.3 Hz, 1H), 2.45 - 2.26 (m, 2H), 2.21 - 2.07 (m, 2H), 2.03 - 1.85 (m, 2H), 1.85 - 1.60 (m, 2H); NH and OH wasn't observed
I-283	MS *m/z* 472.3 [M+H]$^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.98 (s, 1H), 9.14 (d, J = 5.4 Hz, 1H), 7.65 (d, J = 5.4 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 4.24 (tt, J = 9.0, 4.0 Hz, 1H), 3.38 – 3.33 (m, 1H), 3.27 (q, J = 9.7 Hz, 2H), 3.01 (dd, J = 10.1, 5.4 Hz, 1H), 2.76 (t, J = 10.2 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.24 – 2.11 (m, 1H), 1.91 (dt, J = 13.0, 4.1 Hz, 1H), 1.82 (dt, J = 13.6, 10.3 Hz, 1H), 1.70 (tq, J = 11.0, 6.4 Hz, 1H), NH and OH not observed.
I-286	MS *m/z* 462.6 [M+H]$^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.70 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 5.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.30 - 7.26 (m, 1H), 4.63 - 4.56 (m, 1H), 3.23 (br d, J = 9.5 Hz, 1H), 2.85 (br d, J = 11.0 Hz, 1H), 2.59 - 2.47 (m, 2H), 2.42 (s, 2H), 2.10 - 1.98 (m, 1H), 1.93 - 1.61 (m, 3H), 1.24 (d, J = 7.3 Hz, 6H); 3H (2OH and NH) wasn't observed
I-288	MS *m/z* 389.4 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.53 (br s, 1 H), 9.79 (s, 1 H), 8.83 (d, J=5.75 Hz, 1 H), 7.69 (d, J=7.38 Hz, 1 H), 7.55 (d, J=7.63 Hz, 1 H), 7.32 - 7.24 (m, 3 H), 4.36 - 4.23 (m, 1 H), 2.17 - 2.05 (m, 2 H), 1.88 - 1.75 (m, 2 H), 1.74 - 1.63 (m, 1 H), 1.52 - 1.32 (m, 4 H) 1.31 - 1.15 (m, 1 H)
I-293	MS *m/z* 484.2 [M+H]$^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.46 (br s, 1 H), 9.78 (s, 1 H), 8.85 (d, J=5.00 Hz, 1 H), 8.15 (s,1 H, formic acid), 7.65 (br d, J=7.50 Hz, 1 H), 7.56 (d, J=7.75 Hz, 1 H), 736 - 7.23 (m, 3 H), 6.68 (t, J=76.42 Hz, 1 H), 4.52 - 4.41 (m, 1 H), 3.95 (t, J=5.75 Hz, 2 H), 3.23 - 3.15 (m, 1 H), 2.86 (d, J=11.01 Hz, 1 H), 2.70 - 2.61 (m, 2 H), 2.17 – 1.97 (m, 3 H), 1.83 - 1.71 (m, 1 H), 1.68 - 1.44 (m, 2 H)

Compound	Spectral Data
I-294	MS *m/z* 450.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.84 (s, 1H), 9.02 (s, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (s, 1H), 4.82 – 4.69 (m, 1H), 4.64 (t, J = 5.5 Hz, 1H), 4.52 (t, J = 5.5 Hz, 1H), 4.08 (s, 1H), 3.72 (s, 1H), 3.39 (td, J = 7.6, 3.4 Hz, 2H), 3.19 – 2.85 (m, 2H), 2.35 (s, 1H), 2.32 – 2.11 (m, 3H), 2.11 – 1.81 (m, 2H).
I-295	MS *m/z* 432.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.56 (br s, 1 H), 9.78 (br s, 1 H), 8.84 (d, J=5.00 Hz, 1 H), 8.18 (s, 1 H, formic acid), 7.65 (d, J=7.75 Hz, 1 H), 7.56 (d, J=7.88 Hz, 1 H), 7.35 - 7.24 (m, 3 H), 4.51 - 4.39 (m, 1 H), 3.16 (d, J=7.88 Hz, 1 H), 2.86 - 2.75 (m, 2 H), 2.25 – 2.13 (m, 2 H), 2.10 - 1.99 (m, 1 H), 1.85 - 1.74 (m, 1 H), 1.65 – 1.42 (m, 2 H), 1.01 (d, J=6.38 Hz, 6 H).
I-300	MS *m/z* 445.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 9.72 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.54 - 7.43 (m, 1H), 7.32 (br d, J = 8.0 Hz, 1H), 7.29 - 7.25 (m, 1H), 4.70 - 4.58 (m, 1H), 3.16 (br d, J = 7.5 Hz, 1H), 2.72 (br s, 1H), 2.23 - 2.05 (m, 5H), 2.02 - 1.92 (m, 2H), 1.92 - 1.84 (m, 1H), 1.84 - 1.65 (m, 4H); NH and OH not observed
I-301	MS *m/z* 408.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.76 (s, 1H), 8.90 (s, 1H), 7.62 – 7.45 (m, 2H), 7.39 – 7.17 (m, 2H), 5.29 (d, J = 49.9 Hz, 1H), 5.07 – 4.91 (m, 1H), 3.65 – 3.49 (m, 1H), 3.45-3.34 (m, 1H), 3.31 – 3.13 (m, 2H), 2.47 – 2.29 (m, 1H), 2.29 – 2.04 (m, 1H). NH and OH not observed
I-302	MS *m/z* 418.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.62 (s, 1H), 8.86 (d, J = 5.9 Hz, 1H), 8.56 (s, 1H, formic acid), 7.56 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 3.68 (d, J = 6.9 Hz, 2H), 3.51 – 3.37 (m, 2H), 2.86 (t, J = 12.5 Hz, 2H), 2.76 (s, 3H), 2.31 – 2.16 (m, 1H), 2.18 – 2.03 (m, 2H), 1.59 (q, J = 12.7 Hz, 2H).
I-303	MS *m/z* 448.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.63 (s, 1H), 8.86 (d, J = 5.7 Hz, 1H), 8.55 (s, 1H, formic acid), 7.57 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.27 (s, 1H), 3.84 (t, J = 5.5 Hz, 2H), 3.68 (d, J = 6.9 Hz, 2H), 3.58 – 3.46 (m, 2H), 3.10 (t, J = 5.6 Hz, 2H), 2.86 (t, J = 12.5 Hz, 2H), 2.32 – 2.16 (m, 1H), 2.15 – 2.04 (m, 2H), 1.63 (q, J = 12.6 Hz, 2H). NH and OH not observed
I-305	MS *m/z* 391.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.70 (s, 1H), 8.94 – 8.75 (m, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 5.4 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.26 (s, 1H), 4.35 (p, J = 8.0 Hz, 1H), 2.69 (t, J = 9.2 Hz, 2H), 2.27 (t, J = 9.7 Hz, 2H), 1.45 (s, 3H). NH and OH not observed
I-306	MS *m/z* 408.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.51 (br s, 1 H), 9.78 (br s, 1 H), 8.85 (d, J=5.63 Hz, 1 H), 8.17 (s, 1 H, formic acid), 7.68 (d, J=7.25 Hz, 1 H), 7.56 (d, J=7.63 Hz, 1 H), 7.35 - 7.26 (m, 3 H), 4.94 (d, J=49.40 Hz, 1 H), 4.75 - 4.58 (m, 1 H), 3.24 (br s, 2 H), 3.12 – 2.98 (m, 1 H), 2.93 - 2.74 (m, 1 H), 2.70 – 2.57 (m, 1 H), 2.41 – 2.27 (m, 1 H), 2.12 - 1.88 (m, 1 H)
I-308	MS *m/z* 419.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.48 (br s, 1H), 9.77 (s, 1H), 8.84 (d, J = 5.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.37 – 7.22 (m, 3H), 4.45 – 4.29 (m, 1H), 3.30 – 3.23 (m, 5H), 2.12 - 2.01 (m, 2H), 1.97 – 1.74 (m, 1H), 1.43 – 1.26 (m, 3H), 1.22 – 1.02 (m, 1H)

Compound	Spectral Data
I-309	MS *m/z* 391.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.48 (br s, 1H), 9.80 (s, 1H), 8.85 (d, J = 5.4 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.34 – 7.26 (m, 3H), 4.52 – 4.35 (m, 1H), 4.15 – 4.04 (m, 1H), 3.89 – 3.78 (m, 1H), 3.43 – 3.24 (m, 2H including H_2O signal), 2.22 – 2.08 (m, 1H), 1.86 – 1.62 (m, 3H)
I-310	MS *m/z* 391.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.50 (br s, 1H), 9.80 (s, 1H), 8.85 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.35 – 7.25 (m, 3H), 4.53 – 4.36 (m, 1H), 4.16 – 4.02 (m, 1H), 3.87 – 3.81 (m, 1H), 3.46 – 3.24 (m, 2H, including H_2O signal), 2.22 – 2.09 (m, 1H), 1.86 – 1.60 (m, 3H)
I-315	MS *m/z* 422.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.77 (s, 1H), 8.86 (d, J = 5.7 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.26 (s, 1H), 5.15 (d, J = 50.5 Hz, 1H), 4.91 (d, J = 15.3 Hz, 1H), 3.11 – 3.00 (m, 1H), 2.74 (d, J = 11.7 Hz, 1H), 2.64 (t, J = 11.1 Hz, 1H), 2.50 – 2.37 (m, 4H), 2.26 – 1.92 (m, 2H).
I-317	MS *m/z* 448.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.76 (s, 1H), 8.87 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.48 (s, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.27 (s, 1H), 4.70 – 4.55 (m, 1H), 3.84 – 3.61 (m, 2H), 3.28 – 3.19 (m, 1H), 3.17 – 3.04 (m, 2H), 3.04 – 2.78 (m, 2H), 2.19 – 1.99 (m, 2H), 1.99 – 1.80 (m, 3H), 1.80 – 1.61 (m, 1H). NH and OH not observed

Example 25

Preparation of Compound I-313



Step 1. 7-Chloro-4-(2-methoxy-4-(trifluoromethyl)phenyl)furo[2,3-*d*]pyridazine

A mixture of 4,7-dichlorofuro[2,3-*d*]pyridazine (351 mg, 1.86 mmol, 1.0 eq.), [2-methoxy-4-(trifluoromethyl)phenyl]boronic acid (490 mg, 2.23 mmol, 1.2 eq.), [1,1'-bis(diphenylphosphino)ferrocence]dichloropalladium(II) (143 mg, 0.19 mmol, 0.1 eq.) and cesium carbonate (1.81 g, 5.57 mmol, 3 eq.) in water (0.33 M) and 1,4-dioxane (0.165 M) was heated at 90°C for 2 hours. Upon completion, the reaction mixture was cooled to room

temperature and diluted with EtOAc, washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford 7-chloro-4-(2-methoxy-4-(trifluoromethyl)phenyl)furo[2,3-*d*]pyridazine (495 mg). The impure isolation was used in next step without further purification. MS *m/z* 329.5, 330.8 $[M+H]^+$.

Step 2. (*R*)-4-(2-Mmethoxy-4-(trifluoromethyl)phenyl)-*N*-(1-methylpiperidin-3-yl)furo[2,3-*d*]pyridazin-7-amine

To a solution of the material from step 1 (417.8 mg, 1.271 mmol, 1 eq.) in DMSO (0.1 M) was added (3*R*)-1-methylpiperidin-3-amine (871 mg, 7.63 mmol, 6 eq.) and DIPEA (1.33 mL,7.63 mmol, 6 eq.). The reaction was heated at 130°C for 24 hours, then cooled to room temperature and diluted with EtOAc, washed with water, saturated $NaHCO_3$ (aq.), and brine. The organics were collected, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 0-70% MeOH (5% NH_3) in DCM to afford (*R*)-4-(2-methoxy-4-(trifluoromethyl)phenyl)-*N*-(1-methylpiperidin-3-yl)furo[2,3-*d*]pyridazin-7-amine as a brown solid (168.5 mg, 32%). MS *m/z* 407.8 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.97 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.19 (s, 1H), 4.60 – 4.44 (m, 1H), 3.88 (s, 3H), 3.48 – 3.37 (m, 1H), 3.08 – 2.92 (m, 1H), 2.64 – 2.52 (m, 5H), 2.21 – 2.10 (m, 1H), 2.07 – 1.95 (m, 1H), 1.90 – 1.76 (m, 1H), 1.75 – 1.62 (m, 1H), 1 NH not observed.

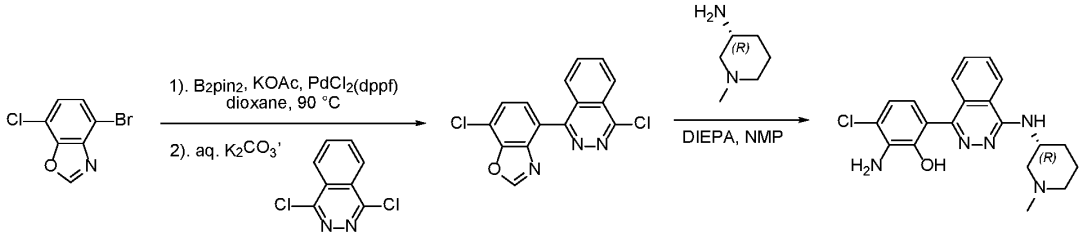
Step 3. (*R*)-2-(7-((1-Methylpiperidin-3-yl)amino)furo[2,3-*d*]pyridazin-4-yl)-5-(trifluoromethyl)phenol

At -78 °C, to a solution of 4-[2-methoxy-4-(trifluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]furo[2,3-*d*]pyridazin-7-amine (100 mg, 0.25 mmol, 1 eq.) in DCM (0.2 M) was added boron tribromide (1 M in DCM) (2.2 ml, 2.21 mmol, 9 eq.). The reaction was kept at -78 °C for 30 min, then allowed to warm to room temperature and stirred for another 1 hour. Upon completion, the reaction was quenched by MeOH and was diluted with DCM. The mixture was vigorously stirred while saturate $NaHCO_3$ (aq.) was added slowly. The organic layer was washed with brine and concentrated *in vacuo*. The crude was purified by preparative reverse phase column (MeCN/water with 0.1% formic acid) to afford 2-[7-[[(3*R*)-1-methyl-3-piperidyl]amino]furo[2,3-*d*]pyridazin-4-yl]-5-(trifluoromethyl)phenol (41.4 mg, 43%) as a yellow solid. MS *m/z* 393.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.32 (d, J = 8.1 Hz, 1H),

7.98 (s, 1H), 7.11 – 7.00 (m, 3H), 4.40 (s, 1H), 3.65 – 3.44 (m, 1H), 3.19 – 3.05 (m, 1H), 2.86 – 2.44 (m, 5H), 2.14 – 1.93 (m, 2H), 1.88 – 1.78 (m, 1H), 1.71 – 1.58 (m, 1H), 1 OH and 1 NH not observed.

Example 26

Preparation of Compound I-163



Step 1. **7-Chloro-4-(4-chlorophthalazin-1-yl)benzo[d]oxazole**

To a dry screw cap vial were added: 7-bromo-4-chloro-1,3-benzoxazole (60 mg, 0.26 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (72 mg, 0.28 mmol), KOAc (51 mg, 0.52 mmol), $Pd(dppf)Cl_2$ (19 mg, 0.03 mmol). The vial was purged with Argon and dioxane (2 ml) was added. The reaction mixture was heated to 90 °C for 2.5h. UPLC showed complete consumption of the starting material. Cooled down to rt, used directly in the next step.

To the mixture above were added: 1,4-dichlorophthalazine (103 mg, 0.52 mmol), K_2CO_3 (72 mg, 0.52 mmol). The vial was purged with Argon for 15 min, and water (0.5 ml) was added. The reaction mixture was heated to 90°C for 3h. UPLC showed complete consumption of the starting material. The reaction was cooled and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient hexane/EtOAc (0-80% EtOAc) to obtain 4-chloro-7-(4-chlorophthalazin-1-yl)-1,3-benzoxazole (48 mg, 59% yield). MS *m/z* 315.7, 317.5 $[M+H]^+$.

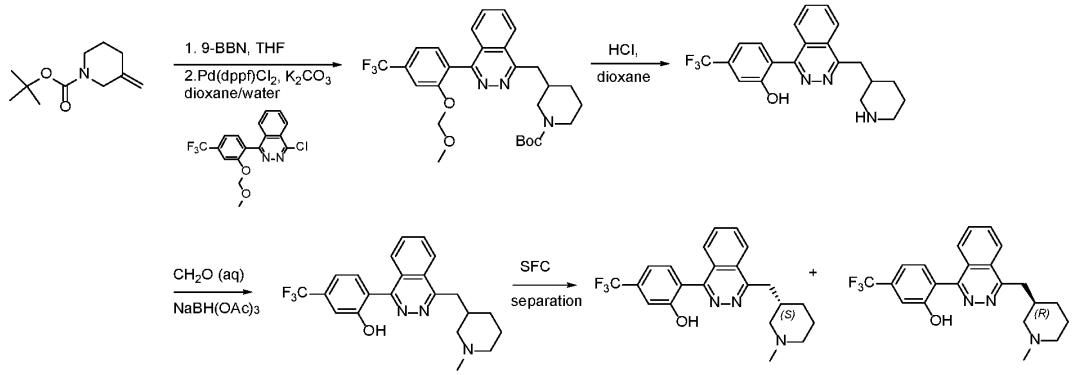
Step 2. (R)-2-Amino-3-chloro-6-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)phenol

To a solution of 4-chloro-7-(4-chlorophthalazin-1-yl)-1,3-benzoxazole (48 mg, 0.15 mmol) in NMP (1.0 mL) was added DIPEA (0.05 mL, 0.30 mmol) and the mixture was heated at 120 °C for 16h. The reaction was cooled to rt, concentrated, the residue was purified by reverse phase chromatography eluting with a gradient ACN/H_2O/formic acid (0-100% ACN) to give (R)-

2-amino-3-chloro-6-(4-((1-methylpiperidin-3-yl)amino)phthalazin-1-yl)phenol (7 mg, 12% yield) as a tan foam. MS *m/z* 384.1, 385.5 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.71 (d, J=8.3 Hz, 1H), 8.30 (td, J=7.8, 1.8 Hz, 1H), 8.15 (td, J=7.8, 0.8 Hz, 1H), 8.03 (br d, J=8.3 Hz, 1H), 7.14 (d, J=8.5 Hz, 1H), 6.76 (d, J=8.3 Hz, 1H), 4.65-4.75 (m, 1H), 3.88-3.98 (m, 1H), 3.61 (br d, J=11.5 Hz, 1H), 3.06-3.16 (m, 2H), 3.02 (s, 3H), 2.22-2.42 (m, 2H), 1.91-2.12 (m, 2H); 4Hs not observed (3 NHs and OH).

Example 27

Preparation of Compounds I-30, I-44, I-96, and I-97



Step 1. tert-Butyl 3-((4-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)phthalazin-1-yl)methyl)piperidine-1-carboxylate

9-BBN (0.5 M in THF, 0.8 mL, 0.38 mmol, 1.5 eq.) was added to tert-butyl 3-methylenepiperidine-1-carboxylate (76 mg, 0.38 mmol, 1.5 eq.) under argon. The seal tube was heated at 65°C for 2hr, then this clear solution was added into a mixture of 1-chloro-4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazine (Intermediate 14b, 93.0 mg, 0.25 mmol, 1.0 eq.) and Pd(dppf)Cl2 (16.6 mg, 0.020 mmol, 0.08 eq.) in K_2CO_3 (2M) in H_2O (0.38 mL, 3.0 eq.) and dioxane (2 mL) under argon. The sealed tube was heated to 90°C o/n. After cooling, the reaction was diluted with EtOAc and $NaHCO_3$ (sat. aq.). The organic phase was washed with H_2O followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-50% EtOAc in DCM to provide tert-butyl 3-[[4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazin-1-yl]methyl]piperidine-1-carboxylate (99 mg, 74 % yield). MS *m/z* 532.2 $[M+H]^+$;

Step 2. 2-(4-(Piperidin-3-ylmethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol

Deprotection of tert-butyl 3-[[4-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]phthalazin-1-yl]methyl]piperidine-1-carboxylate with HCl in dioxane, according to the procedure of Example 11, step 2, provided the title compound as hydrochloride salt. MS *m/z* 388.0 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.79 (d, J=8.3 Hz, 1H), 8.49 (t, J=7.6 Hz, 1H), 8.34 (t, J=7.7 Hz, 1H), 8.24 (d, J=8.3 Hz, 1H), 7.80 (br d, J=8.0 Hz, 1H), 7.51 (br d, J=7.9 Hz, 1H), 7.44 (s, 1H), 3.64-3.66 (m, 3H), 3.38-3.45 (m, 1H), 3.03 (br t, J=12.0 Hz, 2H), 2.65-2.75 (m, 1H), 1.99-2.13 (m, 2H), 1.82 (br d, J=13.6 Hz, 1H), 1.51-1.73 (m, 1H). NH and OH not observed.

Step 3. 2-(4-((1-Methylpiperidin-3-yl)methyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol

Reductive amination of 2-(4-(piperidin-3-ylmethyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol with formaldehyde, according to the procedure of Example 12, step 3. The residue was then purified on prep-HPLC with 5-50% ACN in water with 0.1% formic acid to provide the title compound as formic acid salt. MS *m/z* 402.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.44 (s, 1H, formic acid), 8.28 (d, J=8.3 Hz, 1H), 7.97 (t, J=7.7 Hz, 1H), 7.86 (t, J=7.6 Hz, 1H), 7.70 (d, J=8.3 Hz, 1H), 7.48 (d, J=7.9 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.19 (s, 1H), 3.23-3.39 (m, 2H), 3.11-3.17 (m, 1H), 3.02 (br d, J=10.6 Hz, 1H), 2.43 (s, 3H), 2.25-2.40 (m, 3H), 1.73-1.94 (m, 2H), 1.58 (br d, J=13.6 Hz, 1H), 1.17-1.31 (m, 1H). OH not observed.

Step 4. (S)-2-(4-((1-methylpiperidin-3-yl)methyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol and (R)-2-(4-((1-methylpiperidin-3-yl)methyl)phthalazin-1-yl)-5-(trifluoromethyl)phenol

The racemate from step 3 was separated by SFC purification to provide the following enantiomers (free base):

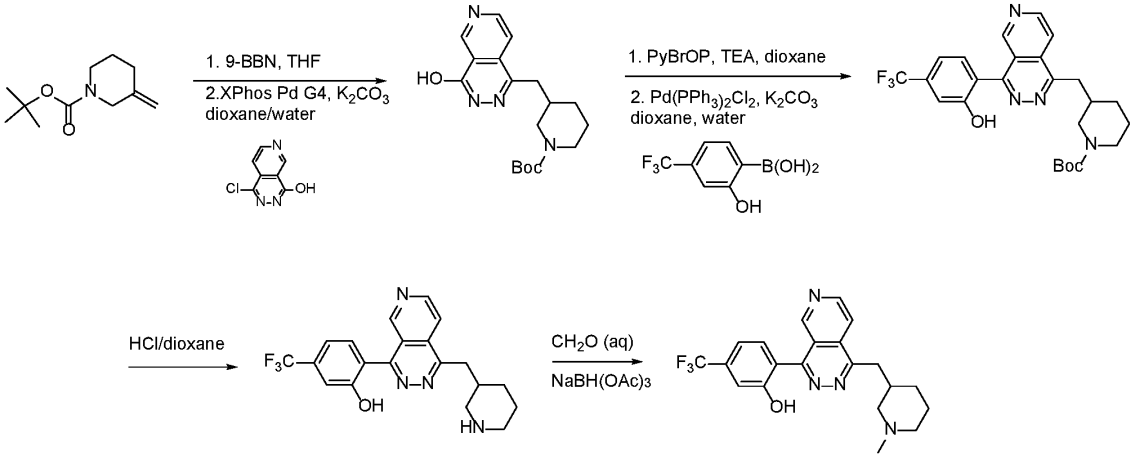
Compound I-96:. MS *m/z* 402.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.41 (d, J=8.4 Hz, 1H), 8.08 (t, J=7.6 Hz, 1H), 7.98 (t, J=7.7 Hz, 1H), 7.82 (d, J=8.1 Hz, 1H), 7.59 (d, J=7.8 Hz, 1H), 7.36 (d, J=7.9 Hz, 1H), 7.30 (s, 1H), 3.35-3.46 (m, 2H), 3.08 (br d, J=11.3 Hz, 1H), 2.99 (br d, J=11.5 Hz, 1H), 2.35-2.45 (m, 4H), 2.14-2.31 (m, 2H), 1.77-1.96 (m, 2H), 1.58-1.71 (m, 1H), 1.26-1.37 (m, 1H). OH not observed.

Compound I-97: MS *m/z* 402.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.41 (d, J=8.4 Hz, 1H), 8.08 (t, J=7.6 Hz, 1H), 7.98 (t, J=7.7 Hz, 1H), 7.82 (d, J=8.3 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.31 (s, 1H), 3.37-3.46 (m, 2H), 3.13 (br d, J=12.8 Hz, 1H), 3.03 (br d,

J=10.8 Hz, 1H), 2.39-2.48 (m, 4H), 2.20-2.35 (m, 2H), 1.80-1.96 (m, 2H), 1.66 (br d, J=13.4 Hz, 1H), 1.15-1.38 (m, 1H). OH not observed.

Example 28a

Preparation of Compounds I-100 and I-118



Step 1. tert-Butyl 3-((4-hydroxypyrido[3,4-d]pyridazin-1-yl)methyl)piperidine-1-carboxylate

tert-Butyl 3-methylenepiperidine-1-carboxylate (318 mg, 1.61 mmol, 1.5 eq.) in 9-BBN (0.5 M in THF, 3.0 mL, 1.5 eq.) was heated at 60°C for 2hr. After cooled to rt, it was added to a mixture of 1-chloro-3H-pyrido[3,4-d]pyridazin-4-one (Intermediate 1a, 195 mg, 1.07 mmol, 1.0 eq.) and XPhos Pd G4 (94mg, 0.10 eq.) in K_2CO_3 (2M) in H_2O (1.6 mL, 3.0 eq.) and dioxane (4 mL) under argon. The sealed tube was heated at 100°C for 4 hr. After cooled to rt, the reaction was diluted with EtOAc, water with a few drop of citric acid (1.0M). The organic phase was washed with H_2O followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% MeOH in DCM to provide tert-butyl 3-[(4-oxo-3H-pyrido[3,4-d]pyridazin-1-yl)methyl]piperidine-1-carboxylate (320 mg, 86% yield). MS *m/z* 345.2 $[M+H]^+$;

Step 2. tert-Butyl 3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl]methyl]piperidine-1-carboxylate

A mixture of tert-butyl 3-[(4-oxo-3H-pyrido[3,4-d]pyridazin-1-yl)methyl]piperidine-1-carboxylate (72 mg, 0.20 mmol, 1.0 eq.) and PyBrOP (150 mg, 0.31 mmol, 1.5 eq.) in Et_3N (64

mg, 3.0 eq.) and dioxane (2 mL) was heated at 100 °C for 2hr. After cooled to rt, [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (86 mg, 2.0 eq.), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.1 eq.) and K_2CO_3 (88 mg, 3.0 eq.) was added under argon, followed by addition of H_2O (0.2 mL). The sealed tube was heated at 100°C for 12 hr. After cooled to rt, the reaction was diluted with EtOAc, water with a few drops of citric acid (1.0M). The organic phase was washed with H_2O followed by brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% MeOH in DCM to provide a mixture of unreacted starting material and tert-butyl 3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl]methyl]piperidine-1-carboxylate (35 mg, 34 % yield), which was then further purified on pre-HPLC, eluting with 20-90%ACN in water (with 0.1% FA).

Step 3. 2-(4-(Piperidin-3-ylmethyl)pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol hydrochloride

Deprotection tert-butyl 3-[[4-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl]methyl]piperidine-1-carboxylate with HCl in dioxane provided the title compound as hydrochloride salt. MS *m/z* 389.1 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.41 (s, 1H), 9.25 (br d, J=5.6 Hz, 1H), 8.40 (br d, J=5.6 Hz, 1H), 7.79 (d, J=7.8 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.40 (s, 1H), 3.54-3.66 (m, 3H), 3.37-3.45 (m, 1H), 2.94-3.06 (m, 2H), 2.64-2.75 (m, 1H), 1.99-2.14 (m, 2H), 1.82 (br d, J=13.9 Hz, 1H), 1.53-1.66 (m, 1H). NH and OH not observed.

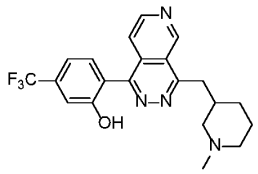
Step 4. 2-(1-((1-Methylpiperidin-3-yl)methyl)pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol

Reductive amination of 2-(1-(piperidin-3-ylmethyl)pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol with formaldehyde, according to the procedure of Example 12, step 3. The residue was then purified on prep-HPLC with 5-50% ACN in water with 0.1% formic acid to provide the title compound as formic acid salt. MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.10 (s, 1H), 8.96 (d, J=5.8 Hz, 1H), 8.37 (s, 1H, formic acid), 8.12 (d, J=5.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 7.21 (s, 1H), 3.36-3.51 (m, 2H), 3.23-3.35 (m, 2H), 2.63-2.75 (m, 5H), 2.50-2.61 (m, 1H), 1.84-1.95 (m, 2H), 1.68 (br d, J=14.3 Hz, 1H), 1.29-1.40 (m, 1H). OH not observed.

Example 28b

Preparation of Compound I-567

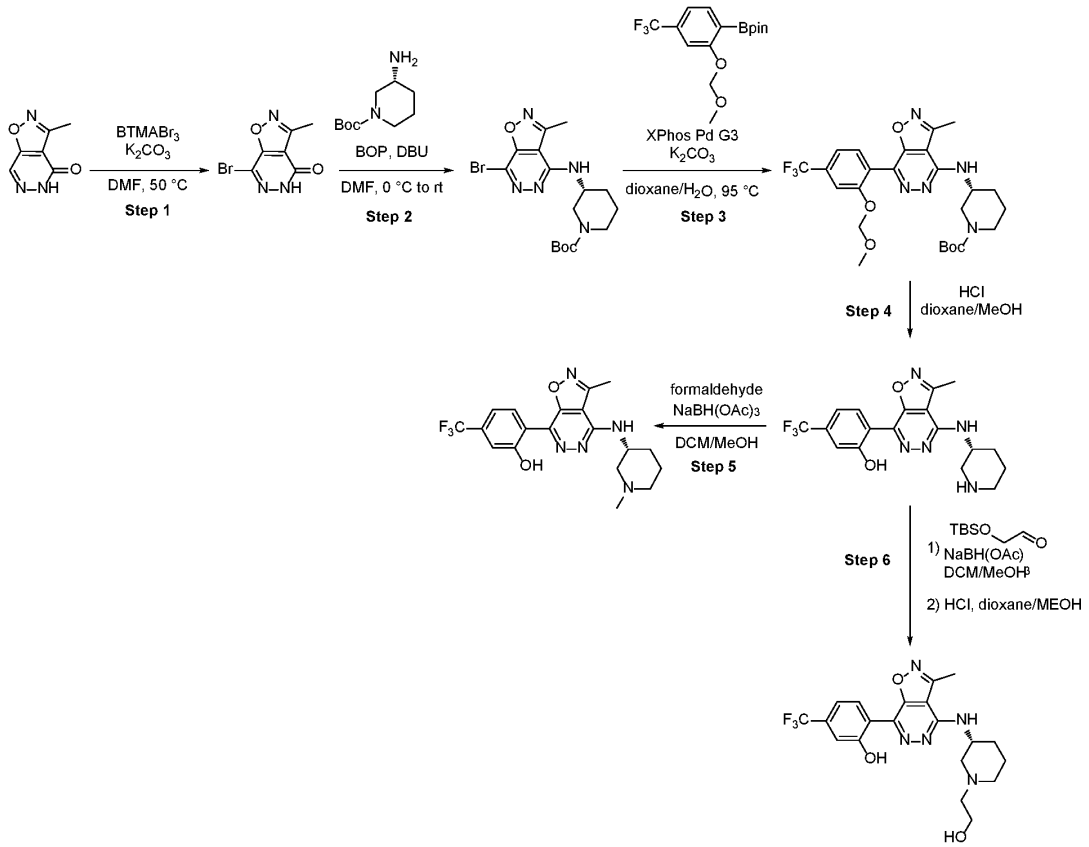
The compound below was prepared in analogous manner according to the procedure of Example 28a, using 4-bromopyrido[3,4-d]pyridazin-1-ol (Intermediate 1b) in place of 1-chloro-3H-pyrido[3,4-d]pyridazin-4-one in step 1.



MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 9.71 (s, 1H), 8.88 (d, J=5.6 Hz, 1H), 7.59 (d, J=5.8 Hz, 1H), 7.51 (d, J=7.9 Hz, 1H), 7.22 (d, J=8.3 Hz, 1H), 7.18 (s, 1H), 3.38 (d, J=7.1 Hz, 2H), 3.12-3.20 (m, 1H), 2.90 (br d, J=9.0 Hz, 1H), 2.68-2.85 (m, 1H), 2.18-2.32 (m, 4H), 1.93-2.09 (m, 2H), 1.82-1.92 (m, 1H), 1.61-1.82 (m, 1H), 1.43-1.59 (m, 1H). OH not observed.

Example 29

Preparation of Compounds I-255 and I-256



Step 1: 7-Bromo-3-methyl-5H-isoxazolo[4,5-*d*]pyridazin-4-one

A suspension of 3-methyl-5*H*-isoxazolo[4,5-*d*]pyridazin-4-one (prepared according to U.S. patent application publication number US2017/73353) (1.45 g, 9.59 mmol) in DMF (21 mL) was added K_2CO_3 (2.65 g, 19.2 mmol), and the mixture was stirred for 10 min at rt. Benzyl trimethylammonium tribromide (7.71 g, 19.2 mmol) was added, and the mixture was heated to 50 °C for 2 h. After cooling to rt, the mixture was filtered through celite, washing with EtOAc. The filtrate was washed with water (2 x 10 mL). The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with sat. $Na_2S_2O_3$, brine, dried (Mg_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 15- 60%) gave a pale yellow solid (1.40 g, 63%%). MS *m/z* 229.9, 231.9 $[M+H]^+$.

Step 2. *t*-Butyl (3*R*)-3-[(7-bromo-3-methyl-isoxazolo[4,5-*d*]pyridazin-4-yl)amino]piperidine-1-carboxylate

To a mixture of 7-bromo-3-methyl-5*H*-isoxazolo[4,5-*d*]pyridazin-4-one (0.250 g, 1.09 mmol) and *t*-butyl (3*R*)-3-aminopiperidine-1-carboxylate (0.653 g, 3.26 mmol) in DMF (4.3 mL) was added DBU (0.34 mL, 2.23 mmol). The mixture was cooled to 0 °C and was added BOP (0.520 g, 1.14 mmol). The reaction mixture was stirred at 0 °C for 5 min before warming to rt. The reaction was stirred 14 h before diluting with DCM/iPrOH (9:1). The mixture was washed with sat. $NaHCO_3$, H_2O, and brine. The organics were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 65%) gave a yellow foam (0.204 g, 46%). MS *m/z* 411.9, 413.8 $[M+H]^+$.

Step 3: *t*-butyl (3*R*)-3-[[7-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-3-methyl-isoxazolo[4,5-*d*]pyridazin-4-yl]amino]piperidine-1-carboxylate

t-Butyl (3*R*)-3-[(7-bromo-3-methyl-isoxazolo[4,5-*d*]pyridazin-4-yl)amino]piperidine-1-carboxylate (0.210 g, 0.509 mmol), 2-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.271 g, 0.815 mmol), and XPhos Pd G3 (0.035 g, 0.041 mmol) were added to a vial and evacuated and refilled with Ar. The mixture was dissolved in dioxane (2.5 mL) and K_2CO_3 (2 M, 0.76 mL, 1.53 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 24 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 65%) gave a yellow foam (0.106 g, 39%). MS *m/z* 538.5 $[M+H]^+$.

Step 4: 2-[3-methyl-4-[[(3*R*)-3-piperidyl]amino]isoxazolo[4,5-*d*]pyridazin-7-yl]-5-(trifluoromethyl)phenol

t-Butyl (3*R*)-3-[[7-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-3-methyl-isoxazolo[4,5-*d*]pyridazin-4-yl]amino]piperidine-1-carboxylate (0.130 g, 0.242 mmol) was dissolved in dioxane (0.5 mL) and added HCl (4M in dioxane, 1.5 mL). The reaction was stirred at rt for 1.5 h. The reaction was diluted with DCM/iPrOH(9:1) and washed with $NaHCO_3$, H_2O, and brine. The organics were dried (Na_2SO_4), filtered and concentrated to give a yellow foam (0.095 g, quant.). MS *m/z* 394.4 $[M+H]^+$.

Step 5: 2-[3-methyl-4-[[(3*R*)-1-methyl-3-piperidyl]amino]isoxazolo[4,5-*d*]pyridazin-7-yl]-5-(trifluoromethyl)phenol formic acid salt

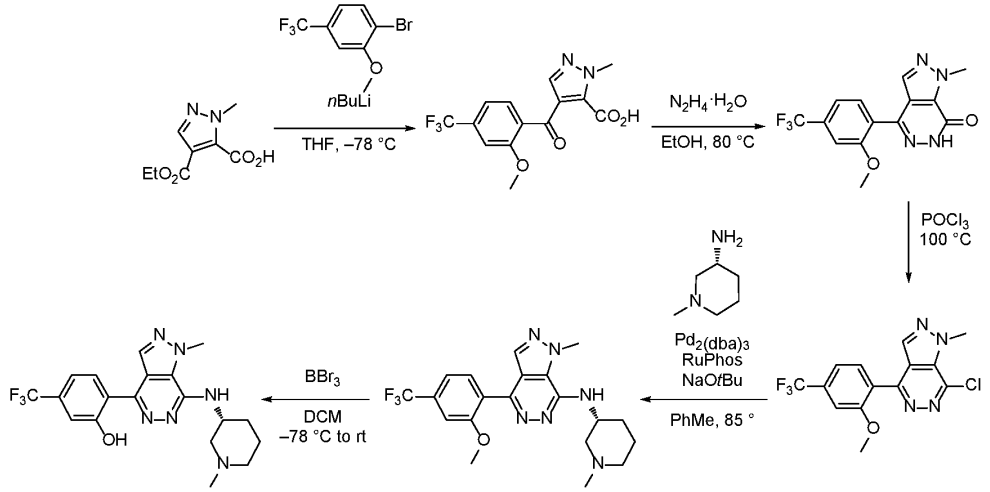
2-[3-Methyl-4-[[(3*R*)-3-piperidyl]amino]isoxazolo[4,5-d]pyridazin-7-yl]-5-(trifluoromethyl)-phenol (0.045 g, 0.11 mmol) in DCM (1.1 mL) was added a methanolic formaldehyde solution (formaldehyde 37% in water, 28 μL, in MeOH 28 μL) followed by $NaBH(OAc)_3$ (0.061 g, 0.23 mmol). The reaction was stirred for 20 min before dilution with DCM. The mixture was then washed with sat. $NaHCO_3$, water, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave the title compound as formic acid salt (0.022 g, 42%). MS *m/z* 408.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 13.28 (s, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.18 (s, 1H, formic acid), 7.39 (d, *J* = 8.1 Hz, 1H), 7.32 (s, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 4.51 – 4.38 (m, 1H), 2.90 (d, *J* = 9.5 Hz, 1H), 2.76 (s, 3H), 2.63 – 2.54 (m, 1H), 2.23 (s, 3H), 2.20 – 2.12 (m, 1H), 2.11 – 2.02 (m, 1H), 1.96 – 1.84 (m, 1H), 1.81 – 1.70 (m, 1H), 1.68 – 1.51 (m, 2H)

Step 6: 2-[3-methyl-4-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]isoxazolo[4,5-*d*]pyridazin-7-yl]-5-(trifluoromethyl)phenol formic acid salt

2-[3-Methyl-4-[[(3*R*)-3-piperidyl]amino]isoxazolo[4,5-*d*]pyridazin-7-yl]-5-(trifluoromethyl)-phenol (0.045 g, 0.11 mmol) in DCM (1.1 mL) was added a 2-[*t*-butyl-(dimethyl)silyl]oxyacetaldehyde solution (0.060 g, in MeOH 27 μL) followed by $NaBH(OAc)_3$ (0.061 g, 0.23 mmol). The reaction was stirred for 20 min before dilution with DCM. The mixture was then washed with sat. $NaHCO_3$, water, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated to give a yellow oil. The oil was then dissolved in dioxane (0.5 mL) and added HCl (4M in dioxane, 1.0 mL). The mixture was stirred at rt for 15 min. The reaction was concentrated and redissolved in DCM. The solution was washed with sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a yellow solid (0.024 g, 43%). MS *m/z* 438.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, *J* = 8.00 Hz, 2 H, with formic acid), 7.39 (d, *J* = 8.25 Hz, 1 H), 7.32 (s, 1 H), 6.73-6.61 (m, 1 H), 4.51 - 4.42 (m, 1 H), 3.53 (t, *J* = 6.19 Hz, 2 H), 2.94 – 2.85 (m, 1 H), 2.76 (s, 3 H), 2.66 – 2.55 (m, 1 H), 2.48 – 2.36 (m, 3 H), 2.35 - 2.01 (m, 3 H), 1.95 – 1.52 (m, 3 H). 3 exchangeable protons not observed.

Example 30

Preparation of Compounds I-144 and I-146



Step 1. 4-[2-Methoxy-4-(trifluoromethyl)benzoyl]-2-methyl-pyrazole-3-carboxylic acid

A solution of 1-bromo-2-methoxy-4-(trifluoromethyl)benzene (1.22 g, 4.79 mmol) in THF (5 mL) was cooled to –78 °C was added *n*BuLi (2.5 M in hexanes, 1.90 mL, 4.79 mmol) and stirred for 40 min. Separately, 4-ethoxycarbonyl-2-methyl-pyrazole-3-carboxylic acid (prepared according to WO2014/27009, 2014, A1) (0.500 g, 2.52 mmol) in THF (16 mL) at –78 °C was added the aryl lithium solution by cannula over ca. 2 min. The reaction was stirred for 5 min before the addition of sat. NH_4Cl at –78 °C. The resulting heterogenous mixture was warmed to rt. The quenched reaction was partitioned between EtOAc/water. The aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes 10% to 1% AcOH in EtOAc) followed by reverse phase chromatography (MeCN:H_2O, 5 to 100%) gave a white solid (0.127 g, 15%). MS *m/z* 329.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 14.16 (br s, 1H), 7.75 (s, 1H), 7.55 (d, *J* = 7.78 Hz, 1H), 7.41 (s, 1H), 7.40 – 7.37 (m, 1H), 3.97 (s, 3H), 3.78 (s, 3H).

Step 2. 4-[2-Methoxy-4-(trifluoromethyl)phenyl]-1-methyl-6*H*-pyrazolo[3,4-*d*]pyridazin-7-one

A mixture of 4-[2-methoxy-4-(trifluoromethyl)benzoyl]-2-methyl-pyrazole-3-carboxylic acid (0.278 g, 0.847 mmol) in EtOH (3.5 mL) was added $N_2H_4·H_2O$ (0.12 mL, 2.54 mL) and 2

drops of acetic acid. The reaction was stirred at 80 °C for 1 h and then cooled in ice-bath. The heterogeneous mixture was filtered and washed with cold EtOH to give a white solid (0.225 g, 82%). MS *m/z* 324.8 $[M+H]^+$.

Step 3: 7-Chloro-4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-pyrazolo[3,4-*d*]pyridazine

$POCl_3$ (0.85 mL) was added to 4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-6*H*-pyrazolo[3,4-*d*]pyridazin-7-one (0.082 g, 0.250 mmol) and heated to 100 °C for 45 min. The reaction was cooled to rt and concentrated to give a pale yellow solid. The solid was dissolved in DCM/MeOH (10:1) and washed with sat. $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography (DCM/MeOH, 0 to 10%) gave a white solid (0.052 g, 60%). MS *m/z* 343.0, 344.8 $[M+H]^+$.

Step 4: 4-[2-Methoxy-4-(trifluoromethyl)phenyl]-1-methyl-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrazolo[3,4-*d*]pyridazin-7-amine formic acid salt

7-Chloro-4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-pyrazolo[3,4-d]pyridazine (0.070 g, 0.200 mmol), $Pd_2(dba)_3$ (0.019 g, 0.020 mol), RuPhos (0.017 g, 0.041 mmol), NaO*t*-Bu (0.039 g, 0.41 mmol), and (3R)-1-methylpiperidin-3-amine (0.028 g, 0.25 mmol) in PhMe (1.0 mL) was heated to 85 °C for 1.5 h. The reaction was diluted with EtOAc and added sat. NH_4Cl. The layers were separated, and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 10%) followed by reverse phase (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a tan solid (0.055 g, 64%). MS *m/z* 421.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H, formic acid), 7.87 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.40 (m, 2H), 6.25 (d, *J* = 6.9 Hz, 1H), 4.44 – 4.36 (m, 1H), 4.33 (s, 3H), 3.85 (s, 3H), 3.05 – 2.96 (m, 1H), 2.70 – 2.58 (m, 1H), 2.27 (s, 3H), 2.23 – 2.09 (m, 2H), 1.94 (br s, 1H), 1.85 – 1.69 (m, 1H), 1.69 – 1.44 (m, 2H)

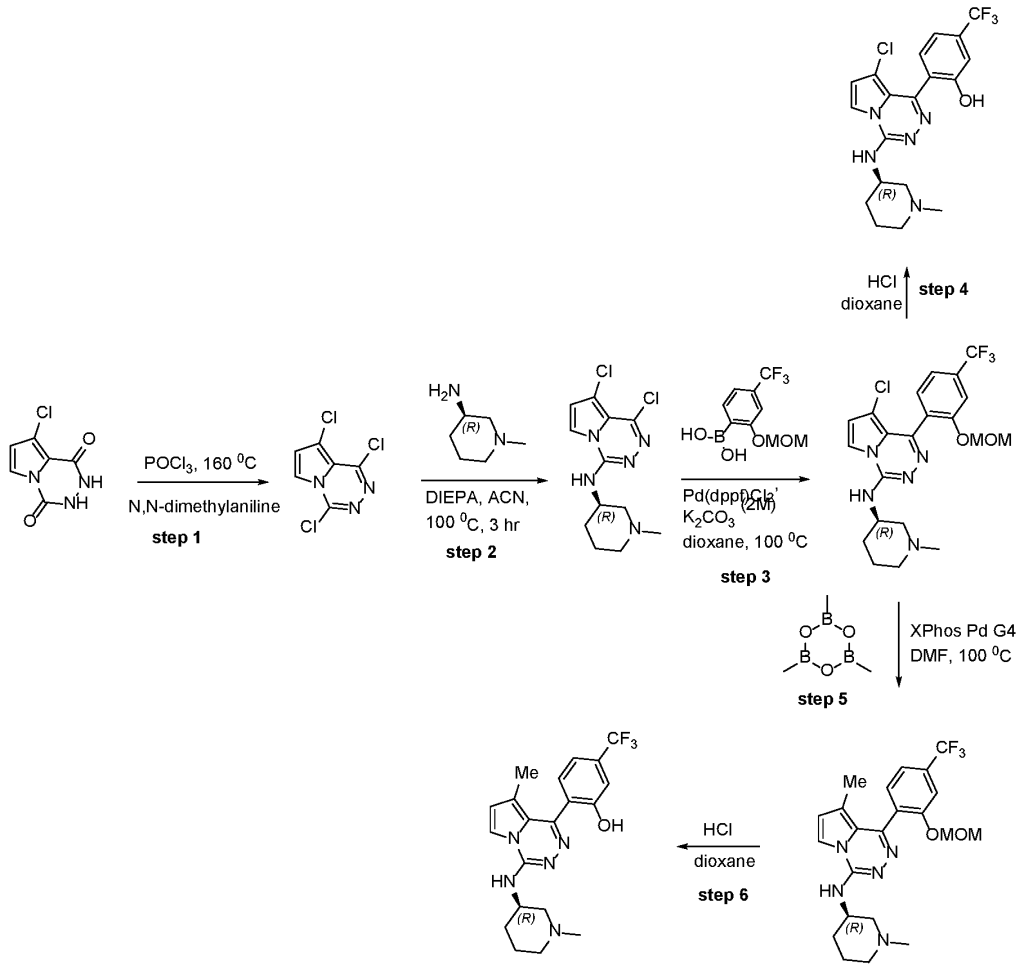
Step 5: 2-[1-Methyl-7-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrazolo[3,4-*d*]pyridazin-4-yl]-5-(trifluoromethyl)phenol formic acid salt

A solution of 4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrazolo[3,4-d]pyridazin-7-amine (0.055 g, 0.13 mmol) in DCM (0.5 mL) was cooled to –78 °C and added BBr_3 (1.0 M in DCM, 1.3 ml, 1.3 mmol). The reaction was stirred at –78 °C for 30 min and let warm to rt, followed by stirring for 1.5 h. The reaction was quenched with

MeOH (0.5 mL) and diluted with DCM (20 mL), stirring 10 min. Sat. $NaHCO_3$ (1.0 mL) was added and vigorously stirred for 15 min. The layers were separated, and the aqueous phase was extracted with DCM. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (1M NH_4OH in MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a yellow solid (0.014 g, 24%). MS *m/z* 407.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.18 (s, 1H, formic acid), 7.31 – 7.21 (m, 2H), 6.56 (d, *J* = 7.5 Hz, 1H), 4.44 – 4.30 (m, 4H), 3.02 – 2.90 (m, 1H), 2.65 – 2.54 (m, 1H), 2.30 – 2.16 (m, 4H), 2.17 – 2.06 (m, 1H), 1.98 – 1.87 (m, 1H), 1.84 – 1.70 (m, 1H), 1.67 – 1.51 (m, 2H). 1H not observed (OH).

Example 31

Preparation of Compounds I-104 and I-321



Step 1. 1,4,8-Trichloropyrrolo[1,2-d][1,2,4]triazine

To a stirred solution of 8-chloro-2,3-dihydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (Intermediate 2c, 2.80 g, 13.7 mmol) in $POCl_3$ (28 mL) was added N,N-dimethylaniline (1.66 g, 13.7 mmol). The reaction mixture was heated at 120 °C for 16 h and then evaporated under reduced pressure to give a residue. The residue was diluted with cold saturated sodium bicarbonate solution (100 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and evaporated under reduced 5 pressure to give a residue which was purified by silica gel column chromatography eluting with EtOAc/hexanes to yield 1,4,8-trichloropyrrolo[1,2-d][1,2,4]triazine (340 mg, 10%). MS *m/z* 221.9, 223.9

$[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ: 8.10 (d, *J* = 4.0 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 1 H).

Step 2. 1,8-Dichloro-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine

To a solution of (3R)-1-methylpiperidin-3-amine dihydrochloride (330 mg, 1.76 mmol) in acetonitrile (5 mL) was added 1,4,8-trichloropyrrolo[1,2-d][1,2,4]triazine (250 mg, 1.12 mmol) and N,N-diisopropylethylamine (520 mg, 4.02 mmol). The mixture was stirred at 100 °C for 3 h. LCMS showed the reaction was completed. The mixture was concentrated to give residue which was purified by silica column (DCM/MeOH = 94/6) to give 1,8-dichloro-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine (155 mg, 46% Yield). MS *m/z* 300.1 $[M+H]^+$.

Step 3. 8-Chloro-1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine

To a solution of [2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]boronic acid (560 mg, 2.24 mmol), potassium carbonate (450 mg, 3.26 mmol), 1,8-dichloro-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine (225 mg, 0.75 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(ii) (110 mg, 0.14 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was stirred at 100°C for 16 hours under N_2. The mixture was cooled to r.t. H_2O was added and the mixture was extracted with EtOAc (100 mL x 3) and combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to give residue which was purified by column chromatography (MeOH/DCM = 5/95) to afford 8-chloro-1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine (245 mg, 69% Yield) as a yellow solid. MS *m/z* 470.2 $[M+H]^+$.

Step 4. 2-[8-Chloro-4-[[(3R)-1-methyl-3-piperidyl]amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl]-5-(trifluoromethyl)phenol

8-Chloro-1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine (70 mg, 0.15 mmol) in dichloromethane (2 mL) was added hydrochloric acid in dioxane (2 mL, 8 mmol, 4 mol/L) at rt. The reaction mixture was stirred at r.t. for 2h. The mixture was concentrated. The mixture was added Sat. $NaHCO_3$ and stirred for 10 min. The mixture was extracted with EtOAc (50 ml x 3). The combined organic layers was washed with brined, dried and concentrated to give residue which was purified by silica column (DCM/MeOH = 95/5) to give 2-[8-chloro-4-[[(3R)-1-methyl-3-

piperidyl]amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl]-5-(trifluoromethyl)phenol (50 mg, 79% Yield) as a solid. MS *m/z* 426.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.91 (s, 1H), 4.50-4.41 (m, 1H), 3.22-3.18 (m, 1H), 2.86-2.82 (m, 1H), 2.44-2.31 (m, 5H), 2.12-2.09 (m, 1H), 1.94-1.90 (m, 1H), 1.79-1.75 (m, 1H), 1.66-1.63 (m, 1H), NH and OH not observed.

Step 5. (R)-1-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-8-methyl-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine

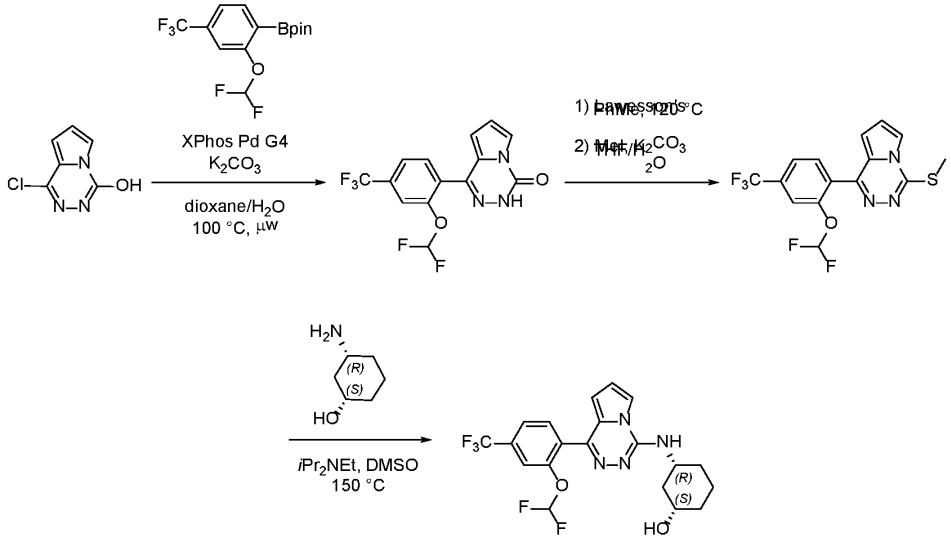
A solution of 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (300 mg, 2.39 mmol), potassium carbonate (120 mg, 0.87 mmol), 8-chloro-1-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine (180 mg, 0.38 mmol) and XPhos Pd G4 (50 mg, 0.057 mmol) in N,N-dimethylformamide (4 mL) and water (0.4 mL) was stirred at 100°C for 12 hours under N_2. Water was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers was washed by H_2O and brine, then dried and concentrated under vacuum to give residue which was purified by silica column (DCM/MeOH = 95/5) to give the mixture (39 mg) of the titled compound and de-Cl of starting material, which was further purified by SFC separation to provide (R)-1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-8-methyl-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine (5 mg) as a yellow solid. MS *m/z* 450.0 $[M+H]^+$.

Step 6. (R)-2-(8-Methyl-4-((1-methylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

(R)-1-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-8-methyl-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine (5 mg) in was stirred in hydrochloric acid in dioxane (4M in dioxane, 0.2 mL) at room temperature for 1 h. The mixture was concentrated, to which Sat. $NaHCO_3$ was added and stirred for 10 min. The mixture was extracted with EtOAc. The combined organic layers were washed with brined, dried and concentrated to give residue which was purified by silica column, eluting with DCM/MeOH to give the title compound (2.5 mg). MS *m/z* 406.2 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 7.73 (d, J=2.9 Hz, 1H), 7.45 (d, J=7.9 Hz, 1H), 7.27 (d, J=7.9 Hz, 1H), 7.20 (s, 1H), 6.74-6.78 (m, 1H), 4.39-4.51 (m, 1H), 3.09-3.21 (m, 1H), 2.69-2.81 (m, 1H), 2.37 (s, 3H), 2.29 (br dd, J=4.8, 3.3 Hz, 2H), 2.02-2.18 (m, 1H), 1.84-1.95 (m, 4H), 1.70-1.81 (m, 1H), 1.59-1.68 (m, 1H), NH and OH not observed

Example 32

Preparation of Compound I-361



Step 1: 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-3*H*-pyrrolo[1,2-*d*][1,2,4]triazin-4-one

To a solution of 1-chloropyrrolo[1,2-d] [1,2,4] triazin-4-ol (Intermediate 2d, step 1, 667 mg, 3.93 mmol, 1.0 eq.) in 1,4-dioxane (12 mL, 0.3 M) and water (3 mL) was added 2-(2-(difluoromethoxy)-4-(trifluoromethyl) phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 7a, 2.00 g, 5.89 mmol, 1.5 eq.), K_2CO_3 (1.10 g, 7.86 mmol, 2.0 eq.) and XPhosPdG4 (333 mg, 0.390 mmol, 0.1 eq.). After the addition was completed, the reaction mixture was stirred at 100 °C for 15 minutes under microwave under N_2. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (PE: EA =10:1 to 5:1) to obtain 1-(2-(difluoromethoxy)-4-(trifluoromethyl) pheny) pyrrolo[1,2-d] [1,2,4] triazin-4(3H)-one (1.20 g, 3.47 mmol, 88% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ: 12.67 (s, 1H), 7.86 – 7.84 (m, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.38 (t, J = 73.2 Hz, 1H), 6.86 – 6.84 (m, 1H), 6.57 (dd, J = 1.2 Hz, 1H).

Step 2. 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-3*H*-pyrrolo[1,2-*d*][1,2,4]triazine-4-thione

To 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-3*H*-pyrrolo[1,2-*d*][1,2,4]triazin-4-

one (1.34 g, 3.88 mmol) in PhMe (16 mL) was added Lawesson's reagent (1.05 g, 2.52 mmol). The mixture was heated to 120 °C for 10 h. The reaction was cooled to rt and filtered to give a white solid (1.15 g, 82%). MS *m/z* 362.3 $[M+H]^+$.

Step 3: 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine

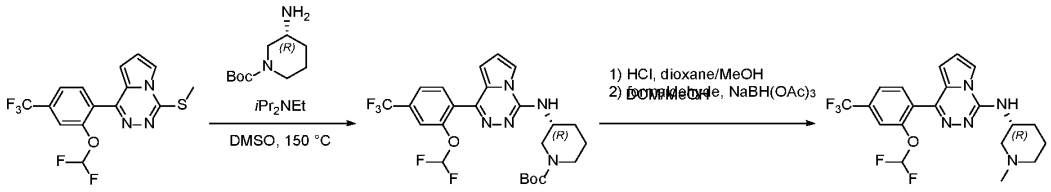
To a solution of 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-3*H*-pyrrolo[1,2-*d*][1,2,4]triazine-4-thione (0.500 g, 1.38 mmol) in THF/H_2O (2:1, 3 mL) was added MeI (0.151 mL, 2.42 mmol) and K_2CO_3 (0.287 g, 2.08 mmol). The mixture was stirred at rt for 2h, then diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 20-60%) gave a white solid (0.419 g, 81%). MS *m/z* 376.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.74 (m, 4 H), 7.39 (t, *J* = 73.17 Hz, 1 H), 7.13 (t, *J* = 3.30 Hz, 1 H), 6.75 (d, *J* = 3.60 Hz, 1 H), 2.87 (s, 3 H).

Step 4: (1*S*,3*R*)-3-[[1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-yl]amino]cyclohexanol

A solution of (difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.070 g, 0.19 mmol) and (1*S*,3*R*)-3-aminocyclohexanol hydrochloride (0.071 g, 0.47 mmol) in DMSO (0.31 mL) was added *i*Pr_2NEt (0.13 mL, 0.75 mmol). The reaction was heated to 150 °C for 36 h, then diluted with DCM/*i*PrOH(9:1) and washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a pale-yellow solid (0.041 g, 50%). MS *m/z* 443.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.85 – 7.73 (m, 2H), 7.73 – 7.66 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 73.8 Hz, 1H), 6.95 (s, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 4.73 (d, *J* = 3.9 Hz, 1H), 4.23 – 4.12 (m, 1H), 3.60 – 3.49 (m, 1H), 2.35 – 2.24 (m, 1H), 2.10 – 1.96 (m, 1H), 1.93 – 1.82 (m, 1H), 1.81 – 1.70 (m, 1H), 1.44 – 1.05 (m, 4H).

Example 33

Preparation of Compound I-322



Step 1: *t*-Butyl (3*R*)-3-[[1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-yl]amino]piperidine-1-carboxylate

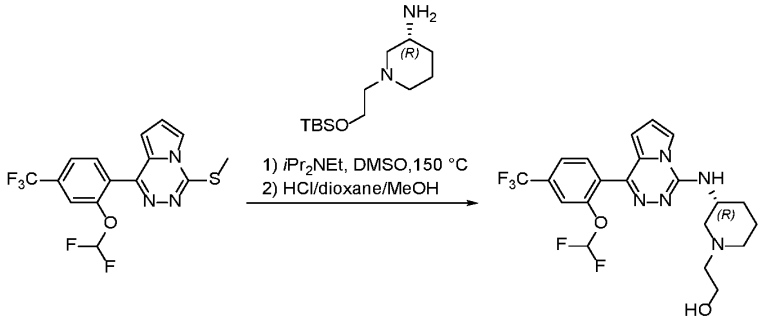
A solution of (difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Example 32, step 1-2, 0.20 g, 0.53 mmol) and *t*-butyl (3R)-3-aminopiperidine-1-carboxylate (0.213 g, 1.07 mmol) in DMSO (1.0 mL) was added *i*Pr$_2$NEt (0.23 mL, 1.60 mmol). The reaction was heated to 150 °C for 36 h. The reaction was diluted with DCM/*i*PrOH(9:1) and washed with brine, water, brine, dried (Na_2SO_4), filtered and concentrated. MS *m/z* 528.3 $[M+H]^+$.

Step 2. 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine

t-Butyl (3*R*)-3-[[1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-yl]amino]piperidine-1-carboxylate (0.281 g, 0.533 mmol) was dissolved in dioxane (0.5 mL) and added HCl (4M in dioxane, 1.5 mL). The reaction was stirred at rt for 1.5 h, then diluted with DCM/iPrOH(9:1) and washed with $NaHCO_3$, H_2O, and brine. The organics were dried (Na_2SO_4), filtered, and concentrated to give a brown oil. The oil was then dissolved in DCM (5 mL) was added a methanolic formaldehyde solution (formaldehyde 37% in water, 0.12 mL, in MeOH 0.12 mL) followed by $NaBH(OAc)_3$ (0.424 g, 1.60 mmol). The reaction was stirred for 10 min before dilution with DCM. The mixture was then washed with sat. $NaHCO_3$, water, and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave an off-white solid (0.063 g, 27%). MS *m/z* 442.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.99 (s, 1H), 7.79 (q, *J* = 7.1 Hz, 2H), 7.70 (s, 1H), 7.37 (t, *J* = 73.92 Hz, 1 H), 7.33 (d, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 6.48 (d, *J* = 3.6 Hz, 1H), 4.38 – 4.25 (m, 1H), 3.08 (d, *J* = 8.9 Hz, 1H), 2.72 (d, *J* = 11.0 Hz, 1H), 2.22 (s, 3H), 2.07 – 1.98 (m, 1H), 1.98 – 1.86 (m, 2H), 1.81 – 1.70 (m, 1H), 1.67 – 1.53 (m, 1H), 1.50 – 1.35 (m, 1H).

Example 34

Preparation of Compound I-325

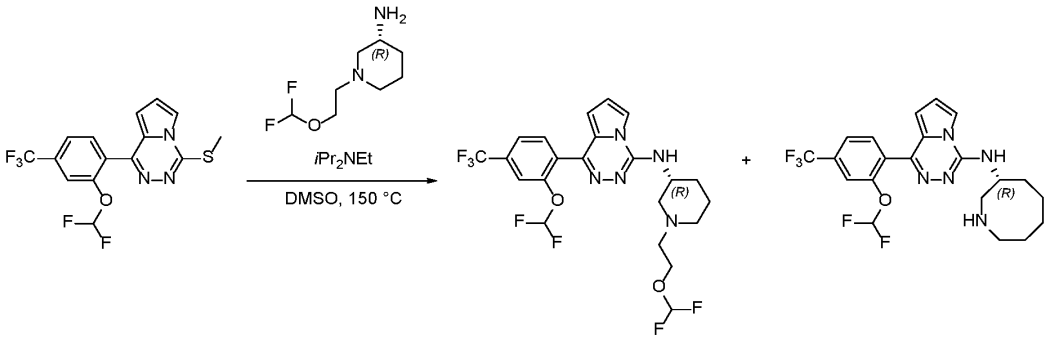


Step 1: 2-[(3*R*)-3-[[1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino]-1-piperidyl]ethanol formic acid salt

A mixture of (difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Example 32, step 1-2, 0.060 g, 0.16 mmol) and (3*R*)-1-[2-[*t*-butyl(dimethyl)silyl]oxyethyl]piperidin-3-amine (0.083 g, 0.32 mmol) in DMSO (0.30 mL) and *i*Pr$_2$NEt (0.11 mL, 0.64 mmol) was heated to 150 °C for 18 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was dissolved in MeOH (0.5 mL) and added HCl/dioxane (4M, 1.0 mL). The reaction was stirred for 1 h. The mixture was concentrated, and the resulting residue was dissolved in DCM/iPrOH (9:1). The solution was washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave an off-white solid (0.031 g, 37%). MS *m/z* 472.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H, formic acid), 7.97 (s, 1H), 7.80 (q, *J* = 8.0 Hz, 2H), 7.70 (s, 1H), 7.37 (t, *J* = 73.54 Hz, 1 H), 7.31 (d, *J* = 7.50 HZ, 1 H), 6.95 (s, 1H), 6.48 (d, *J* = 3.5 Hz, 1H), 4.55 – 4.23 (m, 2H), 3.52 (t, *J* = 6.1 Hz, 2H), 3.17 (d, *J* = 9.8 Hz, 1H), 2.83 (d, *J* = 10.5 Hz, 1H), 2.47 (t, *J* = 6.6 Hz, 2H), 2.13 – 1.98 (m, 3H), 1.82 – 1.70 (m, 1H), 1.68 – 1.39 (m, 2H).

Example 35

Preparation of Compounds I-323 and I-324



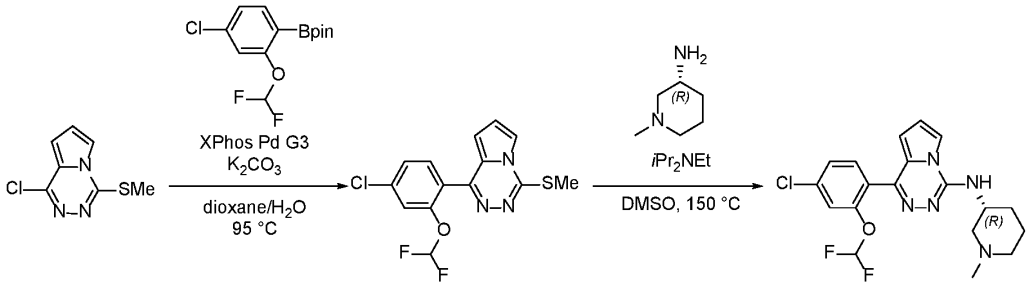
A mixture of (difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Example 32, step 1-2, 0.060 g, 0.16 mmol) and (3*R*)-1-[2-(difluoromethoxy)ethyl]piperidin-3-amine hydrochloride (0.074 g, 0.32 mmol) in DMSO (0.30 mL) and *i*Pr$_2$NEt (0.11 mL, 0.64 mmol) was heated to 150 °C for 18 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) provided 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-[2-(difluoromethoxy)ethyl]-3-piperidyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formic acid salt (0.004 g, 4%) and 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-azocan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formic acid salt, respectively.

Compound I-323: MS *m/z* 522.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H, formic acid), 7.97 (s, 1H), 7.85 – 7.74 (m, 2H), 7.70 (s, 1H), 7.37 (t, *J* = 73.79 Hz, 1 H), 7.34 (d, *J* = 8.13 Hz, 1 H), 6.99 – 6.92 (m, 1H), 6.67 (t, *J* = 77.04 Hz, 1 H), 6.50 – 6.48 (m, 1H), 4.38 – 4.25 (m, 1H), 3.94 (t, *J* = 5.6 Hz, 2H), 3.19 (d, *J* = 10.6 Hz, 1H), 2.86 (d, *J* = 10.8 Hz, 1H), 2.69 – 2.60 (m, 2H), 2.17 – 1.96 (m, 3H), 1.87 – 1.71 (m, 1H), 1.68 – 1.37 (m, 2H).

Compound I-324: MS *m/z* 456.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.05 (d, *J* = 19.76 Hz, 1H), 7.99 (d, *J* = 11.76 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.74 – 7.68 (m, 1H), 7.48 (t, *J* = 7.00 Hz, 1 H), 7.37 (t, *J* = 73.04 Hz, 1 H), 7.03 – 6.94 (m, 1H), 6.55 – 6.47 (m, 1H), 4.50 – 4.40 (m, 1H), 4.29 – 4.10 (m, 1H), 3.99 (d, *J* = 12.3 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.21 – 3.03 (m, 2H), 2.92 – 2.72 (m, 2H), 2.17 (ddd, *J* = 10.4, 4.2, 2.3 Hz, 1H), 1.93 – 1.69 (m, 3H), 1.62 – 1.40 (m, 1H)

Example 36

Preparation of Compound I-356



Step 1: 1-[4-Chloro-2-(difluoromethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine

1-Chloro-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Intermediate 2d, 0.200 g, 1.00 mmol), 2-[4-chloro-2-(difluoromethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (prepared according to the procedure of Intermediate 7a, 0.46 g, 1.50 mmol), and XPhos Pd G3 (0.087 g, 0.100 mmol) were placed in a vial and evacuated and refilled with Ar. Dioxane (5 mL) and aq. K_2CO_3 (2M, 1.50 mL, 3.01 mmol) were added and the solution was sparged with Ar for 5 min. The reaction was heated to 95 °C for 4 h. The reaction was cooled to rt and diluted with EtOAc. The solution was washed with water and brine. The organic phase was dried (Mg_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 60%) gave a tan foam (0.202 g, 59%). MS *m/z* 342.2, 344.2 $[M+H]^+$.

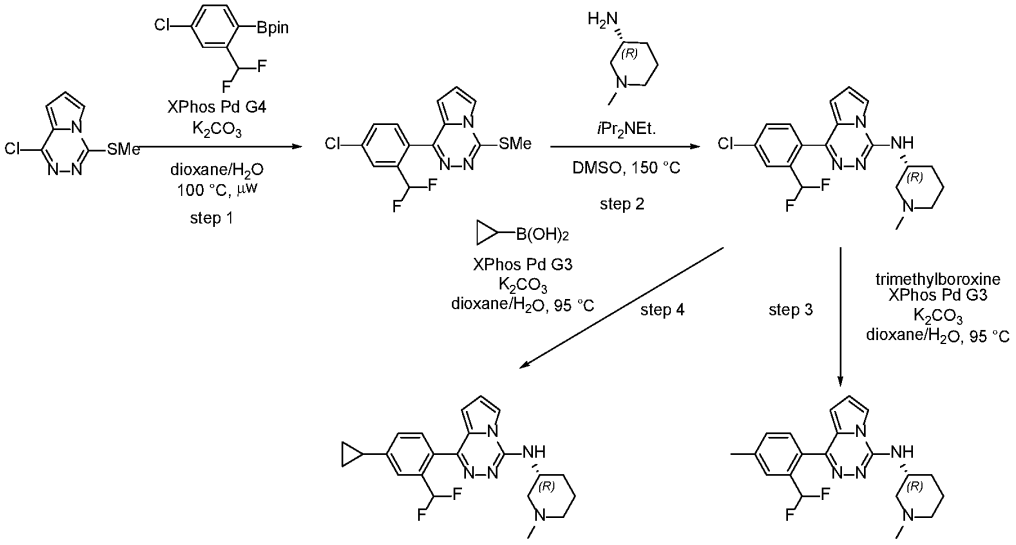
Step 2. 1-[4-Chloro-2-(difluoromethoxy)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine

A mixture of 1-[4-chloro-2-(difluoromethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.042 g, 0.12 mmol) and (3*R*)-1-methylpiperidin-3-amine (0.042 g, 0.37 mmol) in DMSO (0.25 mL) and *i*Pr_2NEt (86 mL, 0.49 mmol) was heated to 150 °C for 30 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.012 g, 24%). MS *m/z* 408.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.64 – 7.55 (m, 1H), 7.48 (s, 2H), 7.29 (s, 1H), 7.26 (t, *J* = 63.5 Hz, 1H), 6.93 (s, 1H), 6.44 (d, *J* = 2.9 Hz, 1H), 4.37 – 4.23 (m, 1H),

3.07 (d, *J* = 8.1 Hz, 1H), 2.72 (d, *J* = 10.3 Hz, 1H), 2.22 (s, 3H), 2.06 – 1.85 (m, 3H), 1.85 – 1.70 (m, 1H), 1.69 – 1.51 (m, 1H), 1.50 – 1.35 (m, 1H).

Example 37

Preparation of Compounds I-443, I-425, and I-446



Step 1: 1-[4-Chloro-2-(difluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine

The title compound was prepared in analogous manner according to the procedure of Example 36, step 1, using 2-(4-chloro-2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 6a) in replace of 2-[4-chloro-2-(difluoromethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. MS *m/z* 326.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.89 (s, 1H),7.81 (d, J= 4.0 Hz, 3H), 7.14 (t, J= 54.8 Hz, 1H),7.14 (d, J = 6.8 Hz, 1H), 6.78(d, J= 3.6 Hz, 1H),2.86 (s, 3H).

Step 2. 1-[4-Chloro-2-(difluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine

A mixture of 1-[4-chloro-2-(difluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.415 g, 1.27 mmol) and (3*R*)-1-methylpiperidin-3-amine (0.364 g, 3.18 mmol) in DMSO (1.3 mL) and *i*Pr$_2$NEt (0.67 mL, 3.82 mmol) was heated to 150 °C for 24 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2

(MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a pale-yellow solid (0.239 g, 48%). MS *m/z* 392.1, 394.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.83 (s, 1H), 7.79 – 7.72 (m, 2H), 7.47 – 7.31 (m, 1H), 7.14 (t, *J* = 55.3 Hz, 1H), 6.97 (s, 1H), 6.56 (s, 1H), 4.40 – 4.27 (m, 1H), 3.10 (d, *J* = 9.1 Hz, 1H), 2.75 (d, *J* = 9.4 Hz, 1H), 2.25 (s, 3H), 2.10 – 1.91 (m, 3H), 1.82 – 1.71 (m, 1H), 1.67 – 1.53 (m, 1H), 1.51 – 1.34 (m, 1H).

Step 3: 1-[2-(Difluoromethyl)-4-methyl-phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine

A mixture of 1-[4-chloro-2-(difluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine (0.040 g, 0.100 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.071 mL, 0.51 mmol), and XPhos Pd G3 (0.009 g, 0.010 mmol) was evacuated and backfilled with Ar (3x) before being diluted with dioxane (0.5 mL) and aq. K_2CO_3 (2M, 0.15 mL, 0.31 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 17 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (10% NH_4OH in MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.026 g, 69%). MS *m/z* 372.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.66 (s, 1H), 7.54 – 7.46 (m, 2H), 6.99 (s, 1H), 6.87 (t, *J* = 58.78 Hz, 1 H), 6.58 (s, 1H), 4.58 – 4.45 (m, 1H), 3.67 – 3.51 (m, 1H), 3.25 – 3.11 (m, 1H), 2.91 – 2.75 (m, 2H), 2.72 (s, 3H), 2.50 (s, 3H), 2.26 – 2.13 (m, 1H), 2.13 – 2.02 (m, 1H), 1.96 – 1.72 (m, 2H). 1H not observed (NH).

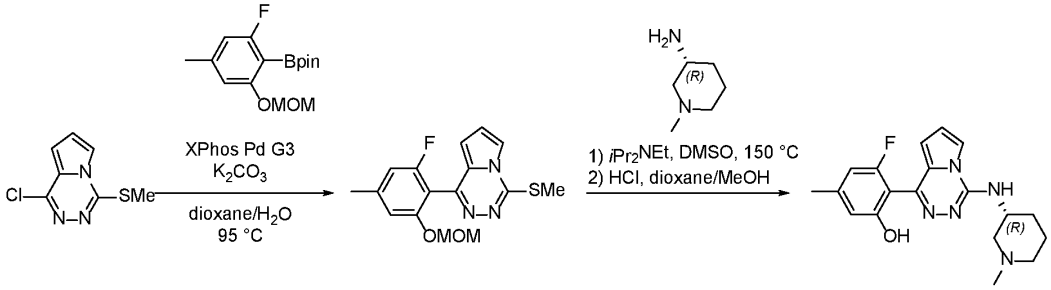
Step 4: 1-[4-Cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3*R*)-1-methyl-3-piperidyl]pyrrolo-[1,2-*d*][1,2,4]triazin-4-amine

A mixture of 1-[4-chloro-2-(difluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine (0.040 g, 0.100 mmol), cyclopropylboronic acid (0.071 mL, 0.51 mmol), and XPhos Pd G3 (0.009 g, 0.010 mmol) was evacuated and backfilled with Ar (3x) before being diluted with dioxane (0.5 mL) and aq. K_2CO_3 (2M, 0.15 mL, 0.31 mmol). The mixture was sparged with Ar for 5 min. The reaction was then heated to 95 °C for 17 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine and concentrated. Purification by chromatography on SiO_2 (10% NH_4OH in MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic

acid in H_2O, 5 to 100%) gave a white solid (0.093 g, 41%). MS *m/z* 398.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.59 – 7.54 (m, 1H), 7.54 – 7.50 (m, 1H), 7.37 – 7.30 (m, 1H), 7.30 – 7.25 (m, 1H), 7.09 (t, *J* = 55.16 Hz, 1H), 6.95 (s, 1H), 6.51 (s, 1H), 4.38 – 4.25 (m, 1H), 3.10 (d, *J* = 8.5 Hz, 1H), 2.75 (d, *J* = 10.4 Hz, 1H), 2.25 (s, 3H), 2.16 – 2.06 (m, 1H), 2.05 – 1.90 (m, 3H), 1.90 – 1.71 (m, 1H), 1.71 – 1.54 (m, 1H), 1.54 – 1.35 (m, 1H), 1.09 – 1.01 (m, 2H), 0.84 – 0.75 (m, 2H).

Example 38

Preparation of Compound I-342



Step 1: 1-[2-Fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine

1-Chloro-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Intermediate 2d, 0.500 g, 2.50 mmol), 2-[2-fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (prepared according to the procedure for Intermediate 5d, 1.11 g, 3.76 mmol), and XPhos Pd G3 (0.216 g, 0.250 mmol) were placed in a vial and evacuated and refilled with Ar. Dioxane (12.5 mL) and aq. K_2CO_3 (2M, 0.3.8 mL, 7.51 mmol) were added and the solution was sparged with Ar for 5 min. The reaction was heated to 95 °C for 15 h, then cooled to rt and diluted with EtOAc. The solution was washed with water and brine. The organic phase was dried (Mg_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 60%) gave a tan solid (0.481 g, 58%). MS *m/z* 334.3 $[M+H]^+$.

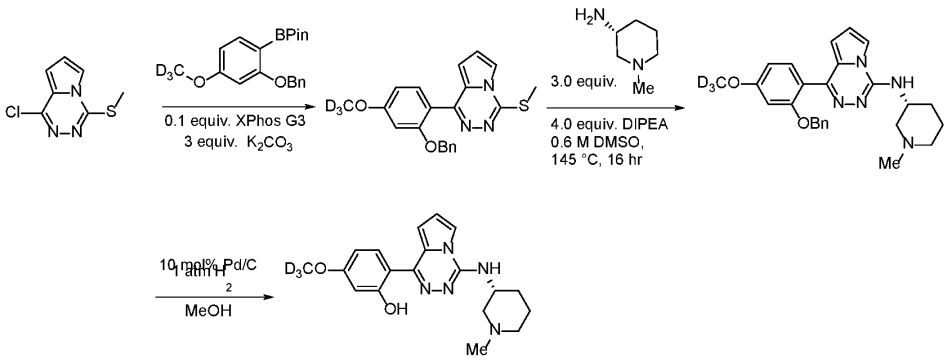
Step 2. 3-Fluoro-5-methyl-2-[4-[[(3*R*)-1-methyl-3-piperidyl]amino]pyrrolo[1,2-*d*][1,2,4]triazin-1-yl]phenol

A mixture of 1-[2-fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.095 g, 0.28 mmol) and (3*R*)-1-methylpiperidin-3-amine (0.098 g, 0.85 mmol) in DMSO (0.47 mL) and *i*Pr$_2$NEt (0.20 mL, 1.1 mmol) was heated to 150 °C for 23

h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with water, brine, dried (Na_2SO_4), filtered and concentrated. The resulting oil was dissolved in MeOH (0.5 mL) and added HCl/dioxane (4M, 1.0 mL). The reaction was stirred for 1 h. The mixture was concentrated, and the resulting residue was dissolved in DCM/iPrOH (9:1). The solution was washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave an off-white solid (0.020 g, 20%). MS *m/z* 356.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (br s, 1H), 7.91 (s, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 6.63 – 6.55 (m, 2H), 6.30 (d, *J* = 4.00 Hz, 1H), 4.36 – 4.21 (m, 1H), 3.13 – 3.02 (m, 1H), 2.76 – 2.62 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.06 – 1.97 (m, 1H), 1.96 – 1.84 (m, 2H), 1.81 – 1.71 (m, 1H), 1.66 – 1.52 (m, 1H), 1.50 – 1.35 (m, 1H).

Example 39a

Preparation of Compound I-501



Step 1: 1-(2-(Benzyloxy)-4-(methoxy-d3)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine

1-Chloro-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Intermediate 2d, 0.67 g, 3.34 mmol, 1.5 eq.), 2-(2-(benzyloxy)-4-(methoxy-d3)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 5e, 0.76 g, 2.23 mmol), and XPhos Pd G3 (0.19 g, 0.22 mmol, 0.1 eq.) were placed in a vial and evacuated and refilled with argon. Dioxane (11 mL) and aq. K_2CO_3 (2M, 3.34 mL, 6.67 mmol, 3 eq.) were added and the solution was sparged with argon for 15 min. The reaction was heated to 95 °C for 6 h, then cooled to rt and diluted with EtOAc. The

reaction mixture was washed with water and brine. The organic phase was dried (Mg_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 60%) gave an brown oil (0.59 g, 69%). MS *m/z* 381.5 $[M+H]^+$; ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.66 – 7.58 (m, 1H), 7.56 – 7.51 (m, 1H), 7.27 (s, 2H), 7.09 – 6.93 (m, 3H), 7.09 – 6.92 (m, 2H), 6.72 – 6.66 (m, 2H), 5.15 (s, 2H), 2.92 (s, 3H).

Step 2. (R)-1-(2-(Benzyloxy)-4-(methoxy-d3)phenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine

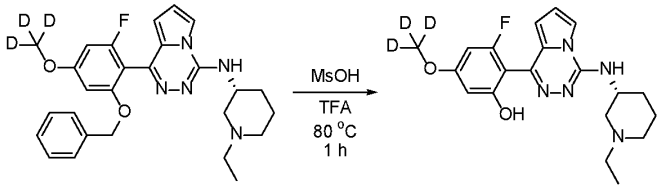
A mixture of 1-(2-(benzyloxy)-4-(methoxy-d3)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (0.16 g, 0.42 mmol) and (3*R*)-1-methylpiperidin-3-amine (0.15 g, 1.27 mmol, 3 eq.) in DMSO (0.71 mL) and *i*Pr_2NEt (0.3 mL, 1.70 mmol, 4 eq.) was heated to 150 °C for 11 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH : DCM, 0 to 10%) gave a brown oil (0.18 g, 94%). MS *m/z* 447.7 $[M+H]^+$.

Step 3: (R)-5-(Methoxy-d3)-2-(4-((1-methylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol

10% Pd/C (0.049 g, 0.047 mmol, 0.1 eq.) was added to a solution of (R)-1-(2-(benzyloxy)-4-(methoxy-d3)phenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine (0.21 g, 0.47 mmol) in MeOH (4.7 mL) under nitrogen. Then the nitrogen in reaction vial was replaced with H_2 (balloon). The reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was passed through a Celite filter to remove Pd/C. The filtrate was concentrated and purified by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave yellow solid (0.063 g, 27%). MS *m/z* 356.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H, Formic acid peak), 7.92 (d, *J* = 7.9 Hz, 1H), 7.87 (s, 1H), 7.25 (s, 1H), 7.05 (s, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.53 (s, 1H), 4.53 – 4.36 (m, 1H), 3.52 – 3.35 (m, 1H), 3.10 – 2.98 (m, 1H), 2.61 (s, 3H), 2.74 – 2.54 (m, 2H), 2.23 – 2.08 (m, 1H), 2.08 – 1.94 (m, 1H), 1.94 – 1.80 (m, 1H), 1.80 – 1.62 (m, 1H). NH and OH not observed.

Example 39b

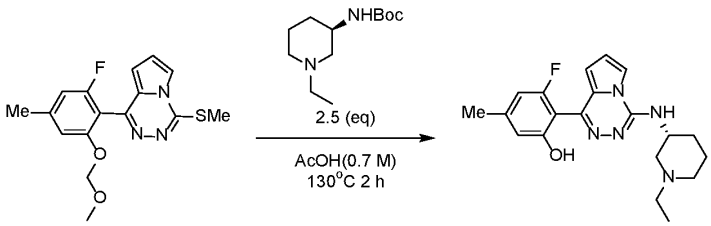
Preparation of Compound I-514



(*R*)-1-(2-(Benzyloxy)-6-fluoro-4-(methoxy-d_3)phenyl)-*N*-(1-ethylpiperidin-3-yl)pyrrolo[1,2-*d*][1,2,4]triazin-4-amine (prepared according to the procedure of Example 46, step 1-3, 14.8 mg, 0.0309 mmol) was dissolved in TFA (1.0 mL) and treated with methanesulfonic acid (29.7 mg, 20.3 μL, 0.309 mmol). The mixture was then stirred at 80 °C for 1 hour. After all starting material has been consumed, the TFA was evaporated, and the acidic residue was diluted and neutralized with saturated $NaHCO_3$ aqueous solution. The aqueous solution was extracted with CH_2Cl_2 (5×). The combined organic layer was then washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution of CH_2Cl_2:MeOH = 100:0 to 80:20) to yield (*R*)-2-(4-((1-ethylpiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-3-fluoro-5-(methoxy-d_3)phenol (10.8 mg, 90% yield) as pale yellow solid. MS *m/z* 389.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 6.94 (s, 1H), 6.56 (s, 1H), 6.42 – 6.30 (m, 2H), 4.54 – 4.44 (m, 1H), 3.06 – 2.92 (m, 1H), 2.80 – 2.64 (m, 2H), 2.57 – 2.32 (m, 3H), 2.21 – 2.11 (m, 1H), 2.02 – 1.92 (m, 1H), 1.87 – 1.79 (m, 1H), 1.76 – 1.65 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). 1 OH and 1 NH signals were not observed.

Example 40

Preparation of Compound I-498



To a solution of 1-(2-fluoro-6-(methoxymethoxy)-4-methylphenyl)-4-(methylthio) pyrrolo[1,2-d][1,2,4]triazine (prepared according to the procedure of Example 38, 100 mg, 0.300

mmol, 1.0 eq.) in AcOH (1 mL) was added tert-butyl (R)-(1-ethylpiperidin-3-yl)carbamate (171 mg, 0.750 mmol, 2.5 eq.). The resulting mixture was stirred at 130 °C for 2 h, then filtered and dried under vacuum. The crude was purified by prep-HPLC ($MeCN/NH_4HCO_3$ in water (10 mmol/L)) to give title product (17.0 mg, 0.05 mmol, 16.7% Yield) as a white solid. MS *m/z* 370.2 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 7.78 (dd, J = 2.8, 1.1 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.61 (s, 1H), 6.57 (d, J = 10.4 Hz, 1H), 6.52 (d, J = 3.9 Hz, 1H), 4.52 – 4.44 (m, 1H), 3.28 – 3.22 (m, 1H), 2.92 – 2.78 (m, 1H), 2.63 – 2.52 (m, 2H), 2.39 – 2.27 (m, 5H), 2.16 – 2.07 (m, 1H), 1.94 – 1.84 (m, 1H), 1.83 – 1.63 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H), NH and OH not observed.

The compounds below were prepared according to the procedure of Example 40 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-106	MS *m/z* 392.1 $M+H]^+$; ^1H NMR (CD_3OD) δ: 8.04 (d, J=8.1 Hz, 1H), 7.81 (d, J=2.5 Hz, 1H), 7.10-7.17 (m, 3H), 6.97 (t, J=3.4 Hz, 1H), 4.28-4.40 (m, 1H), 3.60-3.67 (m, 1H), 2.94-3.20 (m, 1H), 2.52-2.76 (m, 1H), 2.24-2.29 (m, 3H), 2.13-2.23 (m, 1H), 1.91-2.08 (m, 1H), 1.59-1.82 (m, 2H), 1.45-1.57 (m, 1H). NH and OH not observed.
I-326	MS *m/z* 512.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.88 - 7.83 (m, 1H), 7.83 - 7.77 (m, 1H), 7.74 (br d, J = 8.1 Hz, 1H), 7.67 (s, 1H), 7.09-6.73 (m, 2H), 6.57 (d, J = 3.6 Hz, 1H), 4.55 - 4.39 (m, 1H), 4.01 (br d, J = 8.3 Hz, 2H), 3.43 (br t, J = 11.6 Hz, 2H), 2.96 - 2.84 (m, 1H), 2.72 - 2.57 (m, 1H), 2.52 - 2.29 (m, 2H), 2.15 (br d, J = 11.3 Hz, 1H), 1.94 - 1.82 (m, 3H), 1.82 - 1.71 (m, 1H), 1.65 (br s, 3H); NH wasn't observed*m/z*
I-331	MS *m/z* 364.2 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.44 (s, 1H), 8.36-8.57 (m, 1H), 7.69-7.81 (m, 2H), 7.11 (br d, J=3.3 Hz, 1H), 6.94 (br s, 1H), 6.52-6.66 (m, 1H), 4.32 (br s, 1H), 2.69-2.89 (m, 1H), 2.45 (br s, 1H), 2.38 (s, 3H), 1.95-2.07 (m, 1H), 1.86-1.88 (m, 1H), 1.78-1.89 (m, 1H), 1.75-1.92 (m, 1H), 1.65-1.65 (m, 2H), 1.72 (br s, 1H), 1.49-1.61 (m, 1H), 0.91 (br d, J=7.9 Hz, 2H), 0.64 (br d, J=4.6 Hz, 2H)
I-335	MS *m/z* 456.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.97 (br s, 1H), 7.80 (q, J = 7.9 Hz, 2H), 7.70 (s, 1H), 7.37 (t, J = 73.42 Hz, 1 H), 7.36 – 7.27 (m, 1 H), 6.96 (br s, 1H), 6.49 (br s, 1H), 4.41 – 4.21 (m, 1H), 3.59 – 3.41 (m, 1H), 2.71 – 2.55 (m, 1H), 2.43 – 2.29 (m, 1H), 2.11 – 1.88 (m, 2H), 1.85 – 1.65 (m, 2H), 1.65 – 1.31 (m, 3H), 1.10 – 0.90 (m, 3H)
I-337	MS *m/z* 338.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.88 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 4.0 Hz, 1H), 7.06 (t, J = 3.5 Hz, 1H), 6.84 (d, J = 6.5 Hz, 2H), 4.50 – 4.36 (m, 1H), 3.23 – 3.07 (m, 1H), 2.85 – 2.71 (m, 1H), 2.50 – 2.23 (m, 7H), 2.16 – 2.04 (m, 1H), 2.00 – 1.51 (m, 4H). NH and OH not observed.
I-340	MS *m/z* 434.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 7.92 - 7.84 (m, 2H), 7.22 (d, J = 3.6 Hz, 1H), 7.04 (br s, 1H), 6.77 - 6.65 (m, 2H), 4.39 (td,

Compound	Spectral Data
	J = 4.6, 8.8 Hz, 1H), 4.07 - 3.93 (m, 2H), 3.42 (br t, J = 11.7 Hz, 2H), 3.27 (br d, J = 10.5 Hz, 1H), 2.88 (br d, J = 11.1 Hz, 1H), 2.62 (br t, J = 11.6 Hz, 1H), 2.52 - 2.32 (m, 2H), 2.13 (br d, J = 8.5 Hz, 1H), 1.95-1.85 (m, 4H), 1.81 - 1.70 (m, 1H), 1.63 (br d, J = 12.3 Hz, 3H), 1.02 (br d, J = 8.1 Hz, 2H), 0.76 (br d, J = 5.1 Hz, 2H); NH and OH not observed
I-341	MS *m/z* 386.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.95 (br s, 1H), 7.90 (br s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.88 (s, 1H), 6.63 - 6.56 (m, 2H), 6.31 (d, J = 4.13 Hz, 1H), 4.40 (t, J = 6.4 Hz, 1H), 4.36 – 4.22 (m, 1H), 3.52 (q, J = 5.6 Hz, 2H), 3.20 – 3.11 (m, 1H), 2.87 – 2.77 (m, 1H), 2.45 (t, J = 7.75 Hz, 2H), 2.30 (s, 3H), 2.11 – 1.96 (m, 3H), 1.80 – 1.68 (m, 1H), 1.67 – 1.51 (m, 1H), 1.51 – 1.38 (m, 1H).
I-343	MS *m/z* 462.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.04 (br d, J = 7.9 Hz, 1H), 7.89 (br s, 1H), 7.25 - 7.13 (m, 3H), 7.05 (br s, 1H), 4.43 (br s, 1H), 4.01 (br d, J = 8.6 Hz, 2H), 3.42 (br t, J = 11.7 Hz, 2H), 3.32 - 3.25 (m, 1H), 2.89 (br d, J = 10.8 Hz, 1H), 2.74 - 2.51 (m, 1H), 2.40 (br t, J = 9.6 Hz, 2H), 2.18 - 2.09 (m, 1H), 1.87-1.74 (m, 4H), 1.69 - 1.54 (m, 3H). NH and OH not observed
I-344	MS *m/z* 436.5 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 7.89 (s, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.88 (s, 1H), 6.70 – 6.27 (m, 4H), 4.34 – 4.21 (m, 1H), 3.94 (t, J = 5.6 Hz, 2H), 3.19 (d, J = 10.3 Hz, 1H), 2.86 (d, J = 11.4 Hz, 1H), 2.70 – 2.62 (m, 2H), 2.30 (s, 3H), 2.15 – 1.99 (m, 3H), 1.84 – 1.69 (m, 1H), 1.67 – 1.52 (m, 1H), 1.52 – 1.38 (m, 1H)
I-348	MS *m/z* 444.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d : 8.24 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 6.4 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H), 4.35 – 4.28 (m, 1H), 3.08 – 3.06 (m, 1H), 2.73 – 2.70 (m, 1H), 2.22 (s, 3H), 2.04 – 2.00 (m, 1H), 1.97 – 1.87 (m, 2H), 1.78 – 1.75 (m, 1H), 1.66 – 1.56 (m, 1H), 1.48 – 1.38 (m, 1H).
I-352	MS *m/z* 378.4 $[M+H^+]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.09 (d, J = 8.1 Hz, 1H), 7.91 (s, 1H), 7.34 – 7.22 (m, 2H), 7.21 (d, J = 4.0 Hz, 1H), 7.10 (s, 1H), 4.55 – 4.41 (m, 1H), 3.78 – 3.66 (m, 1H), 3.37 – 3.32 (m, 1H), 3.07 – 2.91 (m, 2H), 2.36 – 2.22 (m, 1H), 2.19 – 2.04 (m, 1H), 1.97 – 1.83 (m, 2H). NH and OH not observed
I-353	MS *m/z* 422.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.12 (d, J = 8.1 Hz, 1H), 7.91 (s, 1H), 7.30 – 7.19 (m, 3H), 7.09 (s, 1H), 4.53 – 4.42 (m, 1H), 3.29-3.20 (m, 1H), 3.01 – 2.84 (m, 1H), 2.64 – 2.37 (m, 4H), 2.20 – 2.07 (m, 1H), 2.02 – 1.91 (m, 1H), 1.89 – 1.61 (m, 2H). NH and OH not observed
I-354	MS *m/z* 368.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.99 – 7.78 (m, 2H), 7.23 (d, J = 4.0 Hz, 1H), 7.05 (d, J = 4.0 Hz, 1H), 6.84 (d, J = 5.9 Hz, 2H), 4.42 (dq, J = 9.3, 4.4 Hz, 1H), 3.75 (q, J = 6.1 Hz, 2H), 3.20 (d, J = 10.6 Hz, 1H), 2.79 (s, 1H), 2.68 (qd, J = 13.4, 6.8 Hz, 2H), 2.57 – 2.43 (m, 2H), 2.36 (s, 3H), 2.07 (d, J = 10.6 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.85 – 1.59 (m, 2H). NH and OH peak not observed.
I-355	MS *m/z* 358.2, 360.2 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 7.92 (dd, J = 9.4, 3.1 Hz, 2H), 7.22 (d, J = 3.8 Hz, 1H), 7.10 (t, J = 3.5 Hz, 1H), 7.07 – 6.96

Compound	Spectral Data
	(m, 2H), 4.53 (d, J = 11.3 Hz, 1H), 3.89 – 3.73 (m, 1H), 3.51 – 3.40 (m, 1H), 3.12 – 2.97 (m, 2H), 2.90 (d, J = 2.9 Hz, 3H), 2.34 – 2.13 (m, 2H), 2.05 – 1.83 (m, 2H). NH and OH peak not observed.
I-357	MS $[M+H]^+$ 354.4; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.91 (d, J = 8.6 Hz, 1H), 7.86 (s, 1H), 7.28 – 7.21 (m, 1H), 7.05 (s, 1H), 6.58 (d, J = 8.6 Hz, 1H), 6.53 (s, 1H), 4.52 – 4.37 (m, 1H), 3.83 (s, 3H), 3.47 (d, J = 8.1 Hz, 1H), 3.09 (d, J = 10.3 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.65 (s, 3H), 2.15 (s, 1H), 2.01 (s, 1H), 1.87 (d, J = 11.5 Hz, 1H), 1.80 – 1.67 (m, 1H). NH and OH peak not observed.
I-358	MS $[M+H]^+$ 384.4; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.12 – 8.03 (m, 1H), 8.02 – 7.89 (m, 1H), 7.38 – 7.24 (m, 2H), 7.12 – 7.03 (m, 1H), 6.62 – 6.47 (m, 2H), 4.40 (t, J = 5.1 Hz, 1H), 4.31 – 4.20 (m, 1H), 3.79 (s, 3H), 3.52 (q, J = 5.8 Hz, 2H), 3.20 – 3.10 (m, 1H), 2.82 (d, J = 11.0 Hz, 1H), 2.46 – 2.40 (m, 3H), 2.12 –1.96 (m, 3H), 1.79 – 1.70 (m, 1H), 1.67 – 1.53 (m, 1H), 1.51 – 1.38 (m, 1H).
I-362	MS *m/z* 457.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 7.94 (s, 1H), 7.79 (d, J = 7.0 Hz, 2H), 7.70 (s, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.37 (t, J = 74.7 Hz, 1H), 6.95 (s, 1H), 6.48 (d, J = 3.3 Hz, 1H), 4.28 – 4.14 (m, 1H), 3.30 – 3.21 (m, 4H), 2.46 – 2.45 (m, 1 H), 2.13 – 2.01 (m, 2H), 1.87 – 1.77 (m, 1H), 1.43 – 0.96 (m, 4H)
I-364	MS *m/z* 450.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.20 - 8.10 (m, 1H), 7.97 - 7.88 (m, 1H), 7.28-7.24 (m, 3H), 7.11 - 7.03 (m, 1H), 4.48 - 4.31 (m, 1H), 3.28 - 3.18 (m, 1H), 2.91 - 2.80 (m, 1H), 2.40 (s, 3H), 2.11 - 1.97 (m, 1H), 1.91 - 1.70 (m, 2H), 1.70 - 1.54 (m, 1H), 1.29 (s, 7H); 3H (2OH and NH) wasn't observed.
I-365	MS *m/z* 394.4 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ 8.40 (br s, 1H), 7.77 (br d, J=8.4 Hz, 1H), 7.49 (br s, 1H), 7.40 (br s, 1H), 6.99-7.10 (m, 2H), 4.42-4.67 (m, 1H), 3.79, (br d, J=12.9 Hz, 1H), 3.39-3.47 (m, 1H), 3.10-3.17 (m, 2H), 2.34 (br s, 1H), 2.09-2.26 (m, 1H), 1.79-2.07 (m, 2H). OH and NH not observed.
I-366	MS *m/z* 408.4 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ 8.08 (d, J=8.5 Hz, 1H), 7.92 (br s, 1H), 7.26 (br s, 1H), 7.09 (br s, 1H), 6.84-6.95 (m, 2H), 4.39-4.51 (m, 1H), 3.08-3.30 (m, 1H), 2.69-2.90 (m, 1H), 2.41 (s, 3H), 2.26-2.44 (m, 1H), 2.24-2.38 (m, 1H), 2.03-2.22 (m, 1H), 1.85-2.00 (m, 1H), 1.80 (br d, J=9.9 Hz, 1H), 1.50-1.72 (m, 1H). OH and NH not observed
I-367	MS *m/z* 396.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.06 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.34 (s, 1H), 7.24 (s, 1H), 7.08 (s, 1H), 6.81 (s, 2H), 4.31 (s, 1H), 3.20 – 3.12 (m, 1H), 2.91 (d, J = 11.1 Hz, 2H), 2.32 (s, 3H), 2.26 (s, 2H), 2.19 (d, J = 11.1 Hz, 1H), 2.01 (d, J = 12.1 Hz, 2H), 1.80 – 1.69 (m, 1H), 1.68 – 1.55 (m, 1H), 1.52 – 1.33 (m, 2H), 1.11 (s, 6H).
I-368	MS *m/z* 408.0, 409.7 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 4.0 Hz, 1H), 7.10 (s, 1H), 7.08 – 6.93 (m, 2H), 6.37 – 6.02 (m, 1H), 4.29 (s, 1H), 3.28 – 3.20 (m, 1H), 3.18 (s, 1H), 2.91 (d, J = 11.3 Hz, 1H), 2.81 (t, J = 15.6 Hz, 2H), 2.22 (q, J = 12.1 Hz, 2H), 2.04 (d, J = 12.0 Hz, 1H), 1.76 (d, J = 11.9 Hz, 1H), 1.61 (d, J = 12.9 Hz, 1H), 1.46 (d, J = 12.4 Hz, 1H).

Compound	Spectral Data
I-369	MS *m/z* 388.3, 390.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.91 – 7.76 (m, 2H), 7.14 (d, J = 4.0 Hz, 1H), 6.97 (t, J = 3.3 Hz, 1H), 6.90 (dd, J = 7.5, 1.9 Hz, 2H), 4.33 (s, 1H), 3.64 (hept, J = 5.6 Hz, 2H), 3.10 (d, J = 10.9 Hz, 1H), 2.70 (d, J = 11.1 Hz, 1H), 2.64 – 2.48 (m, 2H), 2.46 – 2.30 (m, 2H), 2.02 – 1.88 (m, 1H), 1.86 – 1.75 (m, 1H), 1.75 – 1.56 (m, 2H). NH and OH peak not observed.
I-370	MS *m/z* 406.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.80 (dd, J= 2.9, 1.2 Hz, 1H), 7.58 (d, J= 7.6 Hz, 1H), 7.39 (d, J= 6.5 Hz, 2H), 6.93 (dd, J= 3.8, 3.0 Hz, 1H), 6.47 (dd, J= 3.9, 1.2 Hz, 1H), 4.47 (s, 1H), 3.84 (d, J= 4.2 Hz, 3H), 3.15 –3.10 (m, 1H), 2.71 (s, 1H), 2.34 (s, 3H), 2.09 –2.07 (m, 2H), 1.89 –1.84 (m, 1H), 1.77 –1.74 (m, 1H), 1.73 –1.62 (m, 1H), 1.62 –1.59 (m, 1H). NH and OH peak not observed
I-371	MS *m/z* 458.2 $[M+H]^+$.; ^1H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H),8.20 (d, J= 8.4 Hz, 1H), 8.01 (d, J= 2.0 Hz, 1H),7.91 (d, J=7.6 Hz, 1H),7.35 (d, J= 8.0 Hz, 1H),6.95 (t, J= 3.2 Hz, 1H),6.39 (d, J= 3.6 Hz, 1H),4.30(s, 1H),3.14 (d, J= 6.0 Hz, 1H),2.84 (d, J= 9.2 Hz, 1H),2.40 (d, J= 5.2Hz, 2H),2.05 (d, J= 9.6 Hz, 1H),1.95-1.91(m, 2H), 1.82-1.76 (m, 1H), 1.65-1.54 (m, 1H),1.49-1.44(m, 1H), 1.02(t, J= 7.2 Hz, 3H).
I-372	MS *m/z* 410.7 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.91 - 7.77 (m, 1H), 7.12 - 7.00 (m, 2H), 7.00 - 6.90 (m, 1H), 6.59 - 6.48 (m, 1H), 4.56-4.45 (m, 1H), 3.27 - 3.13 (m, 1H), 2.82 - 2.71 (m, 1H), 2.46-2.24 (m, 5H), 2.16-2.07 (m, 1H), 1.97-1.86 (m, 1H), 1.85 - 1.56 (m, 2H); 1H (NH) is not observed.
I-373	MS *m/z* 438.4 $[M+H]^+$; ^1H NMR (CD_3OD) δ 8.10 (d, J=8.5 Hz, 1H), 7.97 (d, J=2.1 Hz, 1H), 7.27 (d, J=4.0 Hz, 1H), 7.10 (t, J=3.4 Hz, 1H), 6.88-6.94 (m, 2H), 4.44 (dt, J=8.3, 4.3 Hz, 1H), 3.70-3.79 (m, 2H), 3.16-3.21 (m, 1H), 2.73-2.81 (m, 1H), 2.58-2.72 (m, 2H), 2.39-2.51 (m, 2H), 2.03-2.10 (m, 1H), 1.86-1.93 (m, 1H), 1.68-1.82 (m, 2H). OH and NH not observed.
I-376	MS *m/z* 429.4$[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.99 (s, 1H), 7.87 – 7.73 (m, 2H), 7.70 (s, 1H), 7.39 (t, J = 65.7 Hz, 1H), 7.37 (s, 1 H), 6.96 (s, 1H), 6.50 (s, 1H), 4.35 – 4.26 (m, 1H), 4.06 (d, J = 9.5 Hz, 1H), 3.83 (d, J = 10.3 Hz, 1H), 3.45 – 3.36 (m, 2H), 2.18 – 2.08 (m, 1H), 1.85 – 1.61 (m, 3H)
I-377	MS *m/z* 368.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ 7.98 – 7.79 (m, 2H), 7.24 (s, 1H), 7.12 – 6.97 (m, 1H), 6.64 – 6.46 (m, 2H), 4.52 – 4.33 (m, 1H), 3.83 (s, 3H), 3.43 – 3.40 (m, 1H), 3.04 (d, *J* = 1.6 Hz, 1H), 2.79 (d, *J* = 4.9 Hz, 2H), 2.55 (m, 2H), 2.25 – 2.08 (m, 1H), 1.96 (d, *J* = 1.3 Hz, 1H), 1.88 – 1.64 (m, 2H), 1.35 – 1.18 (m, 3H). NH and OH peak not observed
I-378	MS *m/z* 442.2 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.90 - 7.72 (m, 3H), 7.67 (s, 1H), 7.00 - 6.98 (m, 1H), 6.93 (t, J = 75 Hz, 1H) 6.57 (dd, J = 0.9, 4.0 Hz, 1H), 4.34 - 4.17 (m, 1H), 3.00 - 2.82 (m, 1H), 2.48 - 2.35 (m, 1H), 2.25 - 2.12 (m, 1H), 2.02 - 1.84 (m, 2H), 1.64 - 1.48 (m, 1H), 1.48 - 1.27 (m, 2H), 1.25 - 1.09 (m, 1H); 3H (NH) not observed
I-379	MS *m/z* 412.5 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.80 (s, 1H), 6.96 (s, 1H), 6.56 (s, 1H), 6.52 (s, 1H), 6.46 (d, J = 10.7 Hz, 1H), 4.62 - 4.54 (m, 1H), 3.93 -3.78 (m, 3H), 3.47 – 3.37 (m, 1H), 3.21 -3.10 (m, 2H), 3.01 -

Compound	Spectral Data
	2.84 (m, 2H), 2.28 – 2.19 (m, 1H), 2.15 – 2.06 (m, 1H), 2.02 - 1.76 (m, 3H), 1.07 - 0.98 (m, 2H), 0.81 – 0.69 (m, 2H). 3H not observed (NH and 2 OH).
I-380	MS *m/z* 382.5 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.80 (s, 1H), 6.97 (s, 1H), 6.65 – 6.38 (m, 3H), 4.60 - 4.49 (m, 1H), 3.80 - 3.68 (m, 1H), 2.98 – 2.87 (m, 2H), 2.81 (s, 3H), 2.29 – 2.19 (m, 1H), 2.17 – 2.08 (m, 1H), 1.99 – 1.78 (m, 4H), 1.07 – 0.99 (m 2H), 0.81 – 0.70 (m, 2H). 2H not observed (NH and OH).
I-388	MS *m/z* 415.1 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.80 (dd, J = 2.8, 1.0 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.66 – 7.61 (m, 1H), 7.58 – 7.54 (m, 1H), 6.88 (dd, J = 3.8, 3.1 Hz, 1H), 6.81 (t, J = 73.1 Hz, 1H), 6.47 (dd, J = 3.9, 1.0 Hz, 1H), 4.76 – 4.69 (m, 1H), 4.08 – 3.92 (m, 2H), 3.87 – 3.75 (m, 2H), 2.41 – 2.29 (m, 1H), 2.14 – 2.02 (m, 1H). NH not observed.
I-389	MS *m/z* 403.2 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d_4) δ 7.71 (dt, *J* = 3.1, 1.7 Hz, 1H), 7.68 (s, 1H), 7.65 – 7.61 (m, 1H), 7.57 – 7.54 (m, 1H), 6.89 (dd, *J* = 3.8, 2.9 Hz, 1H), 6.81 (t, *J* = 73.4 Hz, 1H), 6.46 (dd, *J* = 3.8, 1.1 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.67 – 3.58 (m, 1H), 3.50 – 3.37 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H). NH peak not observed.
I-392	MS *m/z* 420.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.81 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 2H), 6.95 (t, J = 3.6 Hz, 1H), 6.51 (dd, J = 4.0 Hz,1.2 Hz, 1H), 4.56 – 4.50 (m, 1H), 3.83 (s, 3H), 3.65 – 3.59 (m, 1H), 3.27 – 3.19 (m, 1H), 2.99 – 2.88 (m, 2H), 2.76 – 2.62 (m, 2H), 2.22 – 2.19 (m, 1H), 2.08 – 2.03 (m, 1H), 1.92 – 1.77 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H). NH and OH not observed
I-393	MS *m/z* 410.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.87 (t, J= 3.7 Hz, 1H), 7.58 (d, J= 8.0 Hz, 1H), 7.33 (d, J= 7.7 Hz, 1H), 7.30 – 7.18 (m, 2H), 6.91 (dd, J= 5.3, 3.3 Hz, 1H), 4.27 (s, 1H), 2.88 (m, 2H), 2.21 (s, 3H), 2.03-1.99(m, 1H), 1.96 – 1.85 (m, 1H), 1.81 – 1.69 (m, 1H), 1.66 – 1.35 (m, 2H), 1.23 (s, 1H).
I-394	MS *m/z* 459.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.90 (t, J= 3.8 Hz, 1H), 7.83 – 7.71 (m, 2H), 7.65 (s, 1H), 7.45 (d, J= 7.6 Hz, 1H), 7.40 (t, J= 72.9 Hz, 1H), 6.93 (d, J= 3.4 Hz, 1H), 4.31 (s, 1H), 3.15 – 2.67 (m, 2H), 2.26 (s, 3H), 2.02 – 1.99 (m , 2H), 1. 80 – 1.76 (m, 1H), 1.71 – 1.34 (m, 2H), 1.24 (d, J= 3.4 Hz, 1H).
I-395	MS *m/z* 397.3 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.91 (br s, 1H), 7.13 - 7.04 (m, 2H), 7.00 (br s, 1H), 6.61 (br s, 1H), 4.37 (br s, 1H), 4.18 (br d, J = 8.7 Hz, 1H), 3.89 (br d, J = 11.1 Hz, 1H), 3.56 - 3.40 (m, 2H), 2.23 (br s, 1H), 1.90 - 1.76 (m, 3H); 2H (OH and NH) wasn't observed
I-399	MS *m/z* 393.4 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d6) δ 8.19 – 8.06 (m, 2H), 7.79 – 7.62 (m, 1H), 7.31 – 7.25 (m, 2H), 7.22 (d, J = 3.5 Hz, 1H), 7.13 – 7.08 (m, 1H), 4.85 – 4.71 (m, 1H), 4.24 – 4.09 (m, 1H), 3.61 – 3.50 (m, 1H), 2.32 – 2.24 (m, 1H), 2.07 – 1.99 (m, 1H), 1.92 – 1.83 (m, 1H), 1.81 – 1.70 (m, 1H), 1.45 – 1.22 (m, 3H), 1.19 – 1.06 (m, 1H). 1H not observed (OH).
I-400	MS *m/z* 407.4 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d6) δ 8.14 (d, J = 8.5 Hz, 1H), 8.06 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.20 (d, J = 3.7 Hz, 1H), 7.10 (t, J = 3.4 Hz, 1H), 4.26 – 4.16 (m, 1H), 3.30 – 3.23 (m, 4H),

Compound	Spectral Data
	2.46 – 2.41 (m, 1H), 2.05 (br d, J = 10.1 Hz, 2H), 1.85 – 1.78 (m, 1H), 1.41 – 1.27 (m, 3H), 1.13 – 1.01 (m, 1H). 1H not observed (OH).
I-401	MS *m/z* 379.4 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d6) δ 8.14 – 8.08 (m, 2H), 7.58 (d, J = 7.3 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.18 (d, J = 3.8 Hz, 1H), 7.10 (t, J = 3.4 Hz, 1H), 4.34 – 4.24 (m, 1H), 4.06 (dd, J = 10.6, 3.0 Hz, 1H), 3.83 (d, J = 11.1 Hz, 1H), 3.33 – 3.25 (m, 2H), 2.13 (d, J = 11.3 Hz, 1H), 1.83 – 1.60 (m, 3H). 1H not observed (OH).
I-402	MS *m/z* 345.2, *m/z*347.2 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ 8.01 – 7.76 (m, 2H), 7.23 (d, J = 4.0 Hz, 1H), 7.07 (t, J = 3.6 Hz, 1H), 6.99 (d, J = 7.8 Hz, 2H), 4.31 (dt, J = 9.3, 4.9 Hz, 1H), 4.16 (dd, J = 10.8, 4.1 Hz, 1H), 3.89 (d, J = 10.8 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.44 (t, J = 9.9 Hz, 1H), 2.23 (s, 1H), 1.82 (q, J = 12.1 Hz, 3H). NH and OH peak not observed.
I-403	MS *m/z* 416.4, 418.3 $[M+H]^+$. ^1H NMR (500 MHz, MeOD) δ 8.00 – 7.84 (m, 2H), 7.21 (d, J = 4.1 Hz, 1H), 7.05 (q, J = 3.1 Hz, 1H), 6.97 (d, J = 7.5 Hz, 2H), 4.37 (tt, J = 8.8, 3.8 Hz, 1H), 3.35 (s, 2H), 2.97 – 2.85 (m, 1H), 2.50 (t, J = 8.6 Hz, 1H), 2.45 (d, J = 2.7 Hz, 1H), 2.03 (q, J = 9.2 Hz, 1H), 1.93 – 1.73 (m, 2H), 1.66 – 1.54 (m, 1H), 1.34 – 1.30 (m, 1H), 1.28 (s, 3H), 1.22 (d, J = 15.7 Hz, 3H). NH and OH peaks not observed.
I-404	MS *m/z* 386.3, 388.3 $[M+H^+]^+$; ^1H NMR (500 MHz, MeOD) δ 7.95 – 7.81 (m, 2H), 7.19 (d, J = 4.0 Hz, 1H), 7.14 – 7.04 (m, 1H), 6.99 (d, J = 7.1 Hz, 2H), 4.50 (s, 1H), 3.55 (d, J = 11.0 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.22 – 3.10 (m, 1H), 2.78 (d, J = 9.9 Hz, 1H), 2.70 (d, J = 3.0 Hz, 1H), 2.21 (d, J = 12.1 Hz, 1H), 2.05 (d, J = 13.9 Hz, 1H), 1.94 – 1.82 (m, 1H), 1.74 (d, J = 11.9 Hz, 1H), 1.27 (dd, J = 6.6, 3.7 Hz, 6H). NH and OH peak not observed.
I-405	MS *m/z* 433.30 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d4) δ 8.13 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 1.2 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.09 (dd, J = 4.1, 3.0 Hz, 1H), 4.44 (p, J = 8.0 Hz, 1H), 3.15 – 3.07 (m, 2H), 2.52 – 2.40 (m, 2H). OH and NH not observed.
I-406	MS *m/z* 379.4 $[M+H^+]^+$; ^1H NMR (500 MHz, Methanol-d4) δ 8.16 (d, J = 8.2 Hz, 1H), 7.92 (s, 1H), 7.30 – 7.21 (m, 3H), 7.12 – 7.05 (m, 1H), 4.23 (p, J = 8.0 Hz, 1H), 2.71 – 2.62 (m, 2H), 2.33 – 2.23 (m, 2H), 1.45 (s, 3H). NH and OH not observed
I-407	MS *m/z* 363.4 $[M+H]^+$; ^1H NMR (CD_3OD) δ 7.81-7.85 (m, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.55 (s, 1H), 7.49 (d, J=7.8 Hz, 1H), 6.96 (t, J=3.1 Hz, 1H), 6.50 (d, J=3.8, Hz, 1H), 4.49 (br s, 1H), 3.85 (s, 3H), 3.14-3.29 (m, 1H), 2.71-2.84 (m, 1H), 2.28-2.43 (m, 5H), 2.08-2.16 (m, 1H), 1.85-1.95 (m, 1H), 1.74-1.83 (m, 1H), 1.57-1.70 (m, 1H). NH not observed.
I-412	MS *m/z* 442.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.16 – 8.04 (m, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.18 (s, 1H), 7.10 (s, 1H), 6.18 (d, J = 56.4 Hz, 1H), 4.40 – 4.25 (m, 1H), 3.27 – 3.19 (m, 1H), 2.95 – 2.87 (m, 1H), 2.87 – 2.75 (m, 2H), 2.29 – 2.14 (m, 2H), 2.10 – 1.99 (m, 1H), 1.83 – 1.70 (m, 1H), 1.68 – 1.37 (m, 2H)
I-414	MS *m/z* 424.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.90 - 7.78 (m, 1H), 7.11 - 7.02 (m, 2H), 7.00 - 6.92 (m, 1H), 6.59 - 6.52 (m, 1H), 4.62 - 4.44 (m, 1H), 3.51 - 3.39 (m, 1H), 3.07 - 2.91 (m, 1H), 2.81 - 2.63 (m, 2H),

Compound	Spectral Data
	2.57 - 2.39 (m, 2H), 2.23 - 2.08 (m, 1H), 2.03 - 1.90 (m, 1H), 1.90 - 1.66 (m, 2H), 1.28 - 1.17 (m, 3H); NH and OH not observed
I-415	MS *m/z* 440.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.95 (br s, 1H), 8.08 - 7.80 (m, 1H), 7.24 - 6.97 (m, 3H), 6.85 - 6.48 (m, 1H), 4.76 - 4.58 (m, 1H), 4.24 - 4.00 (m, 1H), 4.00 - 3.84 (m, 2H), 3.82 - 3.57 (m, 1H), 3.19 - 2.84 (m, 2H), 2.42 - 1.78 (m, 5H); 1H was overlapped with solvent peak. 3H (2OH and NH) not observed
I-416	MS *m/z* 428.3 $[M+H]^+$;^{1}H NMR (400 MHz, METHANOL-d4) δ 8.36 (br s, 1H), 7.40 (br s, 2H), 7.33 - 7.13 (m, 2H), 5.47 - 5.22 (m, 1H), 4.10 - 3.79 (m, 2H), 3.57 - 3.36 (m, 1H), 3.27 - 3.12 (m, 1H), 3.04 (br s, 3H), 2.79 - 2.62 (m, 1H), 2.33 - 2.06 (m, 1H); 1H was overlapped with solvent peak, 2H (OH & NH) not observed
I-417	MS *m/z* 468.4 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.00 - 7.66 (m, 1H), 7.24 - 6.86 (m, 3H), 6.74 - 6.39 (m, 1H), 4.76 - 4.52 (m, 1H), 3.99 - 3.74 (m, 1H), 3.61 - 3.40 (m, 1H), 3.05-2.90 (m, 4H), 2.39 - 1.95 (m, 3H), 1.94 - 1.73 (m, 1H), 1.35 (br s, 6H). OH and NH not observed.
I-420	MS *m/z* 395.2 [M-H]-; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.09 - 7.77 (m, 1H), 7.33 - 6.88 (m, 3H), 6.83 - 6.55 (m, 1H), 4.42 - 4.11 (m, 1H), 2.67 (br s, 2H), 2.31 (br s, 2H), 1.45 (br s, 3H); NH and OH not observed
I-421	MS *m/z* 343.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.96 – 7.77 (m, 1H), 7.07 – 6.90 (m, 1H), 6.73 – 6.45 (m, 3H), 4.42 – 4.31 (m, 1H), 4.24 – 4.11 (m, 1H), 3.93 – 3.83 (m, 1H), 3.57 – 3.38 (m, 2H), 2.46 – 2.16 (m, 4H), 1.91 – 1.70 (m, 3H). 2 H not observed (NH and OH).
I-422	MS *m/z* 357.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.01 – 7.70 (m, 1H), 7.13 – 6.88 (m, 1H), 6.83 – 6.45 (m, 3H), 4.32 – 4.16 (m, 1H), 3.81 – 3.67 (m, 1H), 2.54 – 2.23 (m, 4H), 2.23 – 2.04 (m, 1H), 2.04 – 1.93 (m, 1H), 1.93 – 1.80 (m, 1H), 1.54 – 1.17 (m, 4H). 3H not observed (NH and 2 OH).
I-423	MS *m/z* 369.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.95 – 7.75 (m, 1H), 7.05 – 6.88 (m, 1H), 6.66 – 6.35 (m, 3H), 4.43 – 4.24 (m, 1H), 4.23 – 4.13 (m, 1H), 3.93 – 3.80 (m, 1H), 3.58 – 3.38 (m, 2H), 2.30 – 2.15 (m, 1H), 1.95 – 1.72 (m, 4H), 1.09 - 0.96 (m, 2H), 0.81 – 0.67 (m, 2H). 2H not observed (NH and OH).
I-424	MS *m/z* 383.3 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.90 – 7.78 (m, 1H), 7.04 – 6.90 (m, 1H), 6.70 – 6.38 (m, 3H), 4.31 – 4.13 (m, 1H), 3.83 – 3.66 (m, 1H), 2.51 – 2.35 (m, 1H), 2.22 – 2.06 (m, 1H), 2.04 – 1.78 (m, 3H), 1.55 – 1.19 (m, 4H), 1.08 - 0.95 (m, 2H), 0.85 – 0.66 (m, 2H). 3H not observed (NH and 2 OH).
I-426	MS *m/z* 426.3 $[M+H^+]^+$; ^{1}H NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.90 (s, 2H), 7.06 (t, J = 56 Hz,1H), 7.01 (s, 1H), 6.61 (d, J = 3.8 Hz, 1H), 4.55 – 4.42 (m, 1H), 3.23 – 3.10 (m, 1H), 2.77 (s, 1H), 2.47 – 2.27 (m, 5H), 2.18 – 2.03 (m, 1H), 1.98 – 1.84 (m, 1H), 1.84 – 1.71 (m, 1H), 1.71 – 1.55 (m, 1H). NH peak not observed.
I-427	MS *m/z* 413.3. $[M+H^+]^+$; ^{1}H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.08 (t, J = 56 Hz, 1H), 6.99 (t, J = 3.3 Hz,

Compound	Spectral Data
	1H), 6.64 – 6.54 (m, 1H), 4.27 (p, J = 8.3 Hz, 1H), 2.66 (m, J = 2.1 Hz, 2H), 2.35 – 2.21 (m, 2H), 1.44 (s, 3H). NH and OH peaks not observed.
I-428	MS *m/z* 406.6 $[M+H]^+$; ^1H NMR (500 MHz, METHANOL-d4) δ 7.88 (br s, 1H), 7.10 - 7.03 (m, 2H), 7.03 - 6.66 (m, 2H), 6.53 (d, J = 3.5 Hz, 1H), 4.72 - 4.47 (m, 1H), 3.96 - 3.74 (m, 1H), 3.53 - 3.38 (m, 1H), 3.22 - 3.01 (m, 2H), 2.93 (s, 3H), 2.50 (s, 3H), 2.32 - 2.14 (m, 2H), 2.04 - 1.82 (m, 2H); 1H (NH) wasn't observed
I-430	MS *m/z* 480.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.86 (br s, 1H), 7.15 - 7.05 (m, 2H), 7.00 (br s, 1H), 6.58 (br s, 1H), 4.60 (br s, 1H), 4.06 (br s, 2H), 3.96 - 3.75 (m, 1H), 3.54 - 3.38 (m, 3H), 3.02 - 2.81 (m, 2H), 2.35 - 2.20 (m, 1H), 2.19 - 1.67 (m, 8H); 2H (OH and NH) wasn't observed
I-431	MS *m/z* 406.6 $[M+H]^+$; ^1H NMR (500 MHz, ACETONITRILE-d3) δ = 8.07 - 7.77 (m, 1H), 7.27 - 6.83 (m, 2H), 6.76 (br s, 1H), 6.27 (br s, 1H), 4.72 (br s, 1H), 4.47 (br s, 1H), 3.37 - 2.68 (m, 4H), 2.60 - 2.33 (m, 3H), 2.01 (br s, 4H), 1.84 - 1.64 (m, 3H); 1H (OH or NH) wasn't observed
I-432	MS *m/z* 376.2, 378.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 7.93 (s, 1H), 7.25 (s, 1H), 6.98 (d, J = 9.3 Hz, 1H), 6.88 (d, J = 11.9 Hz, 2H), 6.35 (s, 1H), 4.32 – 4.28 (m, 1H), 3.16 (d, J = 3.9 Hz, 1H), 3.12 – 3.07 (m, 1H), 2.76 – 2.71 (m, 1H), 2.24 (s, 3H), 2.00 – 1.96 (m, 3H), 1.78 – 1.74 (m, 1H), 1.61 (d, J = 12.9 Hz, 1H), 1.43 (d, J = 12.7 Hz, 1H).
I-433	MS *m/z* 390.1, 392.1 $[M+H^+]^+$; ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.01 – 6.90 (m, 1H), 6.81 (d, J = 7.4 Hz, 2H), 6.53 (d, J = 4.0 Hz, 1H), 4.55 – 4.44 (m, 1H), 3.35 (s, 1H), 2.99 – 2.84 (m, 1H), 2.65 (d, J = 7.8 Hz, 2H), 2.45 – 2.30 (m, 2H), 2.21 – 2.08 (m, 1H), 1.99 – 1.88 (m, 1H), 1.79 (d, J = 11.9 Hz, 1H), 1.68 (d, J = 11.5 Hz, 1H), 1.19 (t, J = 7.3 Hz, 3H). NH and OH peak not observed.
I-434	MS *m/z* 363.2, 365.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.14 (s, 1H), 7.90 (s, 1H), 7.01 (s, 1H), 6.86 (d, J = 7.1 Hz, 1H), 6.67 (s, 1H), 4.24 (p, J = 8.1 Hz, 1H), 2.66 (t, J = 9.2 Hz, 2H), 2.28 (t, J = 9.8 Hz, 2H), 1.44 (s, 3H). NH and OH peak not observed.
I-437	MS *m/z* 369.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.29 (br s, 1H), 7.74 (br d, J=7.6 Hz, 1H), 7.36 (br s, 2H), 6.99-7.08 (m, 2H), 4.17-4.28 (m, 1H), 3.65-3.77 (m, 1H), 3.55-3.64 (m, 1H), 1.31 (d, J = 6.3 Hz, 3H). OH and NH not observed.
I-438	MS *m/z* 383.3 $[M+H]^+$; ^1H NMR (CD_3OD) δ 8.07 (br d, J=8.6 Hz, 1H), 7.91 (br s, 1H), 7.26 (br s, 1H), 7.11 (br s, 1H), 6.87-6.94 (m, 2H), 3.72 (s, 2H), 1.29-1.38 (m, 6H). OH and NH not observed.
I-440	MS *m/z* 421.6 $[M+H]^+$; ^1H NMR (CD_3OD) δ 7.67-7.81 (m, 3H), 7.60 (br s, 1H), 6.94 (t, *J* = 72 Hz, 1H), 6.83 (bs, 1H), 4.12-4.28 (m, 1H), 3.74 (br d, J=13.5 Hz, 1H), 3.47-3.60 (m, 1H), 1.24-1.35 (m, 3H). NH not observed.
I-441	MS *m/z* 426.6 $[M+H]^+$; ^1H NMR (CD_3OD) δ 7.74 (br s, 1H), 7.62 (br d, J=8.3 Hz, 1H), 6.81-6.90 (m, 3H), 4.44 (br s, 1H), 3.13-3.25 (m, 1H), 2.66-2.90 (m, 1H), 2.25-2.47 (m, 5H), 2.09 (br s, 1H), 1.89 (br s, 1H), 1.70-1.84 (m, 1H), 1.50-1.70 (m, 1H)

Compound	Spectral Data
I-447	MS *m/z* 466.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.06 - 7.66 (m, 1H), 7.35 - 6.83 (m, 3H), 6.61 (br dd, J = 2.8, 4.2 Hz, 1H), 4.58 (br s, 1H), 4.03 (br s, 2H), 3.88 (br s, 1H), 3.74 (br s, 3H), 3.29 - 3.13 (m, 1H), 2.95 - 2.71 (m, 2H), 2.42 - 2.19 (m, 2H), 2.19 - 2.02 (m, 2H), 1.98 - 1.75 (m, 2H); 2H (NH and OH) not observed
I-448	MS *m/z* 379.05 $[M+H^+]^+$; ^1H NMR (500 MHz, Methanol-d4) δ 8.15 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 2.9 Hz, 1H), 7.29 – 7.20 (m, 3H), 7.10 – 7.04 (m, 1H), 4.55 (p, J = 7.2 Hz, 1H), 4.40 – 4.33 (m, 1H), 2.54 – 2.46 (m, 1H), 2.28 – 2.20 (m, 1H), 2.06 – 1.73 (m, 4H). OH and NH not observed.
I-449	MS *m/z* 379.40 $[M+H^+]^+$; ^1H NMR (500 MHz, Methanol-d4) δ 8.16 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 2.9 Hz, 1H), 7.30 – 7.21 (m, 3H), 7.10 – 7.04 (m, 1H), 4.79 (p, J = 7.2 Hz, 1H), 4.48 – 4.41 (m, 1H), 2.49 – 2.38 (m, 1H), 2.28 – 2.21 (m, 1H), 2.19 – 2.09 (m, 1H), 2.05 – 1.96 (m, 1H), 1.80 – 1.67 (m, 2H). OH and NH not observed.
I-450	MS *m/z* 407.6 $[M+H^+]^+$; ^1H NMR (500 MHz, Methanol-d4) δ 8.19 (d, J = 8.2 Hz, 1H), 7.94 (s, 1H), 7.35 – 7.22 (m, 3H), 7.14 – 7.05 (m, 1H), 4.59 – 4.45 (m, 1H), 2.30 – 2.16 (m, 2H), 2.02 – 1.88 (m, 1H), 1.80 – 1.65 (m, 2H), 1.61 – 1.50 (m, 1H), 1.47 – 1.23 (m, 6H). OH and NH not observed.
I-454	MS *m/z* 436.2 $[M+H^+]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.74 (dd, J= 2.8Hz, 1.1 Hz, 1H), 7.50 (d, J= 8.2 Hz, 1H), 7.31 (d, J= 6.4 Hz, 2H), 6.90 –6.81 (m, 1H), 6.39 (dd, J= 3.9Hz, 1.1 Hz, 1H), 4.41 (dd, J= 23.0Hz, 19.1 Hz, 1H), 3.73 (s, 3H), 3.68 –3.59 (m, 2H), 3.12 –3.04 (m, 1H), 2.73 –2.63 (m, 1H), 2.60 –2.51 (m, 2H), 2.45 –2.30 (m, 2H), 2.05 –1.90 (m, 1H), 1.85 –1.75 (m, 1H), 1.76 – 1.58(m, 2H). OH and NH not observed.
I-456	MS *m/z* 372.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.85 – 7.72 (m, 1H), 6.95 (s, 1H), 6.58 (s, 1H), 6.36 (s, 2H), 5.49 (s, 1H), 4.51 (m, 1H), 3.82 (m, 3H), 3.60 – 3.46 (m, 1H), 3.17 – 3.02 (m, 1H), 2.80 – 2.68 (m, 2H), 2.65 (s, 3H), 2.17 (m, 1H), 2.04 (m, 1H), 1.95 – 1.69 (m, 2H). OH and NH not observed
I-457	MS *m/z* 402.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.58 – 8.45 (m, 1H), 7.87 – 7.75 (m, 1H), 6.99 – 6.90 (m, 1H), 6.63 – 6.52 (m, 1H), 6.36 (s, 2H), 4.56 – 4.45 (m, 1H), 3.82 (s, 3H), 3.80 (s, 2H), 3.56 – 3.42 (m, 1H), 3.11 – 3.00 (m, 1H), 2.94 – 2.78 (m, 2H), 2.73 – 2.58 (m, 2H), 2.21 – 2.07 (m, 1H), 2.04 – 1.92 (m, 1H), 1.91 – 1.68 (m, 2H). NH and OH peak not observed.
I-458	MS *m/z* 415.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ 8.32 (s, 1H, formic acid proton), 7.96 – 7.86 (m, 1H), 7.84 – 7.77 (m, 1H), 7.77 – 7.70 (m, 1H), 7.66 (s, 1H), 6.98 (d, *J* = 2.6 Hz, 1H), 6.90 (t, *J* = 72 Hz 1H), 6.57 (m, 1H), 4.27 – 4.01 (m, 2H), 4.01 – 3.81 (m, 2H), 2.61 – 2.36 (m, 1H), 2.30 – 2.02 (m, 1H). 1CH signal overlapped with solvent. NH and OH peak not observed.
I-459	MS *m/z* 365.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.14 (m, 1H), 7.96 (s, 1H), 7.33 – 7.19 (m, 3H), 7.08 (s, 1H), 4.83 – 4.77 (m, 1H), 4.17 – 4.02 (m, 2H), 4.01 – 3.84 (m, 2H), 2.54 – 2.37 (m, 1H), 2.25 – 2.09 (m, 1H). NH and OH peak were not observed.
I-462	MS *m/z* 424.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.82 (br s, 1H), 7.06-6.52 (m, 4H), 6.52 (br s, 1H), 5.31 - 5.08 (m, 1H), 3.80 - 3.65 (m,

Compound	Spectral Data
	1H), 3.58 - 3.43 (m, 1H), 3.09 - 2.84 (m, 1H), 2.82 - 2.66 (m, 4H), 2.49 (br s, 4H), 2.19 - 1.93 (m, 1H); NH not observed
I-463	MS *m/z* 436.4 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.85 (br s, 1H), 7.16 - 6.44 (m, 5H), 4.72 - 4.58 (m, 1H), 3.93 (br s, 3H), 3.68 - 3.53 (m, 1H), 3.19 - 2.97 (m, 2H), 2.57 - 2.41 (m, 3H), 2.39 - 1.74 (m, 5H); one H signal was overlapped with solvent peak; NH and OH not observed
I-464	MS *m/z* 391.2 $[M-H]^-$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.88 (br s, 1H), 7.05 (br s, 2H), 6.98 (br s, 2H), 6.50 (br s, 1H), 4.45 - 4.31 (m, 1H), 4.31 - 4.08 (m, 1H), 3.90 (br d, J = 10.6 Hz, 1H), 3.61 - 3.41 (m, 2H), 2.48 (s, 3H), 2.33 - 2.19 (m, 1H), 1.93 - 1.73 (m, 3H); NH wasn't observed
I-465	MS *m/z* 391.2 $[M-H]^-$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.90 - 7.77 (m, 1H), 7.09 - 6.44 (m, 5H), 4.39 - 4.18 (m, 1H), 2.75 - 2.58 (m, 2H), 2.48 (s, 3H), 2.37 - 2.19 (m, 2H), 1.45 (s, 3H); NH and OH not observed.
I-466	MS *m/z* 343.5 $[M+H^+]^+$; ^{1}H NMR (400 MHz, Methanol-d4) δ 7.97 – 7.69 (m, 1H), 7.06 – 6.88 (m, 1H), 6.76 – 6.43 (m, 3H), 4.34 – 4.16 (m, 1H), 2.77 – 2.59 (m, 2H), 2.49 – 2.13 (m, 5H), 1.43 (s, 3H). OH and NH not observed.
I-467	MS *m/z* 369.50 $[M+H^+]^+$; ^{1}H NMR (400 MHz, Methanol-d4) δ 7.90 – 7.72 (m, 1H), 7.05 – 6.86 (m, 1H), 6.67 – 6.38 (m, 3H), 4.35 – 4.14 (m, 1H), 2.75 – 2.56 (m, 2H), 2.34 – 2.18 (m, 2H), 2.00 – 1.82 (m, 1H), 1.43 (s, 3H), 1.11 – 0.96 (m, 2H), 0.75 (s, 2H). OH and NH not observed.
I-469	MS *m/z* 524.1 $[M+H]^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.67 (t, J = 77.2 Hz, 1H), 6.39 (s, 1H), 4.38 – 4.23 (m, 1H), 3.97 – 3.89 (m, 2H), 3.18 (d, J = 9.5 Hz, 1H), 2.91 – 2.81 (m, 1H), 2.71 – 2.58 (m, 2H), 2.17 – 1.99 (m, 3H), 1.82 -1.71 (m, 1H), 1.66 – 1.51 (m, 1H), 1.53 – 1.37 (m, 1H)
I-470	MS *m/z* 502.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.99 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.4 Hz, 1H), 6.94 (s, 1H), 6.38 (s, 1H), 4.40 – 4.29 (m, 1H), 4.11 (s, 1H), 3.20 (d, J = 9.6 Hz, 1H), 2.91 (d, J = 10.3 Hz, 1H), 2.32 – 2.10 (m, 4H), 2.01 (d, J = 10.6 Hz, 1H), 1.81 – 1.68 (m, 1H), 1.68 – 1.54 (m, 1H), 1.54 – 1.36 (m, 1H), 1.10 (s, 6H).
I-471	MS *m/z* 404.3 $[M+H]^+$; ^{1}H NMR (400 MHz, MeOD) δ 7.81 (d, J = 3.1 Hz, 1H), 7.47 (dd, J = 8.7, 2.6 Hz, 1H), 6.95 – 6.86 (m, 3H), 6.77 (t, J = 76 Hz, 1H), 6.53 (d, J = 4.0 Hz, 1H), 4.47 (dq, J = 10.9, 5.0 Hz, 1H), 3.89 (d, J = 2.7 Hz, 3H), 3.22 (d, J = 11.2 Hz, 1H), 2.88 – 2.71 (m, 1H), 2.47 – 2.28 (m, 5H), 2.10 (d, J = 12.5 Hz, 1H), 1.90 (dd, J = 11.7, 6.4 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.64 (d, J = 11.7 Hz, 1H). NH not observed
I-472	MS/ *m/z* 391.3 $[M+H]^+$; ^{1}H NMR (400 MHz, MeOD) δ 7.79 (d, J = 3.1 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 6.96 – 6.85 (m, 3H), 6.77 (t, J = 76 Hz, 1H), 6.52 (d, J = 3.7 Hz, 1H), 4.25 (p, J = 8.3 Hz, 1H), 3.89 (d, J = 2.4 Hz, 3H), 2.65 (m, J = 4.3 Hz, 2H), 2.26 (t, J = 9.8 Hz, 2H), 1.43 (d, J = 2.9 Hz, 3H). NH and OH peak not observed.
I-473	MS *m/z* 353.5 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 8.21 – 8.09 (m, 1H), 7.87 (s, 1H), 7.33 – 7.18 (m, 3H), 7.08 (s, 1H), 4.26 – 4.12 (m, 1H),

Compound	Spectral Data
	3.79 – 3.66 (m, 1H), 3.59 – 3.47 (m, 1H), 1.38 – 1.20 (m, 3H). NH and 2 OH peaks not observed.
I-474	MS *m/z* 365.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.14 (d, J = 8.1 Hz, 1H), 7.97 (s, 1H), 7.24 (m, 3H), 7.08 (s, 1H), 4.84 – 4.76 (m, 1H), 4.14 – 4.02 (m, 2H), 3.97 – 3.84 (m, 2H), 2.53 – 2.39 (m, 1H), 2.25 – 2.12 (m, 1H). NH and OH peaks not observed.
I-475	MS *m/z* 476.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.86 (br s, 1H), 7.06 (br s, 2H), 7.03 - 6.61 (m, 2H), 6.52 (br s, 1H), 4.63 (br s, 1H), 4.09 (br d, J = 10.9 Hz, 2H), 4.02 - 3.89 (m, 1H), 3.59 - 3.40 (m, 4H), 3.07 (br d, J = 10.9 Hz, 2H), 2.49 (br s, 3H), 2.36 - 2.16 (m, 2H), 2.16 - 1.74 (m, 6H); NH wasn't observed
I-476	MS *m/z* 464.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.85 (br s, 1H), 7.05 (br s, 2H), 7.02 - 6.59 (m, 2H), 6.51 (br s, 1H), 4.67 (br s, 1H), 3.98 - 3.81 (m, 1H), 3.52 (br d, J = 10.6 Hz, 1H), 3.09-3.02 (m, 4H), 2.49 (br s, 3H), 2.33 - 2.15 (m, 1H), 2.15 - 1.99 (m, 2H), 1.94 - 1.74 (m, 1H), 1.35 (br s, 6H); OH and NH not observed
I-477	MS *m/z* 352.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.02 (br s, 1H), 7.08 (br s, 1H), 6.83 - 6.62 (m, 3H), 3.98 - 3.76 (m, 1H), 3.30 - 3.20 (m, 1H), 3.19 - 2.92 (m, 2H), 2.84 - 2.63 (m, 3H), 2.35 (br s, 4H), 2.14-2.01 (m, 5H), 1.95 - 1.76 (m, 1H); 1H was overlapped with solvent peak. NH and OH wasn't observed
I-479	MS *m/z* 406.6 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.28 (m, 1H, formic acid proton), 8.20 – 8.02 (m, 1H), 7.96 – 7.80 (m, 1H), 7.37 – 7.15 (m, 3H), 7.13 – 6.97 (m, 1H), 4.64 – 4.47 (m, 1H), 3.85 – 3.66 (m, 1H), 3.43 – 3.35 (m, 1H), 3.20 – 3.02 (m, 2H), 2.97 – 2.74 (m, 2H), 2.35 – 2.06 (m, 2H), 2.04 – 1.74 (m, 2H), 1.43 – 1.25 (m, 3H). OH and NH not observed
I-480	MS *m/z* 420.6 $[M+H]^+$; ^1H NMR (400 Hz, Methanol-d4) δ 8.48 (s, 1H, formic acid proton), 8.15 – 8.02 (m, 1H), 7.98 – 7.82 (m, 1H), 7.39 – 7.03 (m, 4H), 4.67 – 4.51 (m, 1H), 3.89 – 3.73 (m, 1H), 3.62 – 3.38 (m, 2H), 3.12 – 2.84 (m, 2H), 2.43 – 2.10 (m, 2H), 2.08 – 1.75 (m, 2H), 1.53 – 1.23 (m, 6H). OH and NH not observed
I-482	MS *m/z* 406.3, 408.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.08 – 6.92 (m, 1H), 6.92 – 6.72 (m, 2H), 6.58 (s, 1H), 4.57-4.70 (m, 2H), 4.05 – 3.81 (m, 3H), 3.66 – 3.53 (m, 1H), 3.25 – 2.97 (m, 2H), 2.38 – 1.79 (m, 5H). NH and OH peak not observed
I-483	MS *m/z* 460.6 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.17 – 8.06 (m, 1H), 7.94 – 7.84 (m, 1H), 7.32 – 7.16 (m, 3H), 7.13 – 7.03 (m, 1H), 4.48 – 4.30 (m, 1H), 3.43 – 3.32 (m, 1H), 3.26 – 3.11 (m, 2H), 3.00 – 2.89 (m, 1H), 2.61 – 2.45 (m, 2H), 2.19 – 2.07 (m, 1H), 1.90 – 1.70 (m, 2H), 1.66 – 1.50 (m, 1H).
I-487	MS *m/z* 460.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.53 (s, 1H, formic acid), 7.87 (s, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.53 (s, 1H), 7.00 (s, 1 H), 6.97 (t, J = 71.8 Hz, 1H), 6.53 (s, 1H), 4.64 – 4.46 (m, 1H), 3.46 – 3.36 (m, 1H), 3.06 – 2.92 (m, 1H), 2.64 – 2.45 (m, 5H), 2.23 – 2.10 (m, 1H), 2.08 – 1.92 (m, 1H), 1.92 – 1.62 (m, 2H). 1H not observed (NH)

Compound	Spectral Data
I-488	MS *m/z* 462.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.85 (br s, 1H), 7.05 (br s, 2H), 7.01 - 6.58 (m, 2H), 6.49 (br s, 1H), 4.52 (br s, 1H), 4.01 (br s, 1H), 3.91 (br s, 2H), 3.84 - 3.67 (m, 1H), 3.64 - 3.39 (m, 2H), 3.20 - 2.99 (m, 1H), 2.74 - 2.57 (m, 2H), 2.48 (s, 3H), 2.34 - 2.15 (m, 2H), 2.04 (br d, J = 3.9 Hz, 2H), 1.94 - 1.70 (m, 2H); NH wasn't observed
I-489	MS *m/z* 412.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.67 (br s, 1H), 6.81 (br s, 1H), 6.58 - 6.35 (m, 3H), 4.33 (br s, 1H), 3.90 - 3.70 (m, 2H), 3.70 - 3.50 (m, 2H), 3.08 - 2.91 (m, 2H), 2.80 - 2.56 (m, 1H), 2.23 (br s, 3H), 2.19 - 2.09 (m, 2H), 2.00 (br s, 2H), 1.88 - 1.39 (m, 5H); 1H (NH) wasn't observed
I-491	MS *m/z* 474.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 8.05 (d, J= 8.1 Hz, 1H), 7.86 (d, J= 1.8 Hz, 1H), 7.78 (d, J= 8.0 Hz, 1H), 6.95 –6.87 (m, 1H), 6.36 (d, J= 3.1 Hz, 1H), 4.44–4.42 (m, 1H), 3.72 –3.61 (m, 2H), 3.09 – 3.08 (m, 1H),2.60–2.57(m, 1H), 2.55–2.50(m, 2H), 2.45 –2.35 (m, 2H), 2.03 – 1.94 (m, 1H), 1.85 –1.76 (m, 1H), 1.74 –1.57 (m, 2H).
I-492	MS *m/z* 405.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 8.11 (d, J= 7.6 Hz, 1H), 7.89 –7.76 (m, 2H), 6.97 (dd, J= 4.0, 2.9 Hz, 1H), 6.42 (dd, J= 3.9, 1.2 Hz, 1H), 4.26 –4.13 (m, 1H), 3.74 (dd, J= 13.8, 4.1 Hz, 1H), 3.55 (dd, J= 13.7, 7.6 Hz, 1H), 1.27 (d, J= 6.3 Hz, 3H).
I-493	MS *m/z* 470.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 7.98 – 7.97 (m, 1H), 7.83 – 7.77(m, 2H), 7.70 (s, 1H), 7.37 (t, J = 73.6 Hz, 1H), 7.31 (d, J = 8.4Hz, 1H), 6.95 (dd, J = 3.6 Hz, 2.8 Hz, 1H), 6.48 (dd, J = 4.0 Hz, 0.8 Hz, 1H), 4.29 – 4.26 (m, 1H), 3.13 – 3.11 (m, 1H), 2.79 – 2.74 (m, 2H), 2.17 – 2.12 (m, 2H), 2.07 – 2.03 (m, 1H), 1.78 – 1.75 (m, 1H), 1.57 – 1.42 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H).
I-494	MS *m/z* 510.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 7.96 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 7.82 – 7.77(m, 2H), 7.70 (s, 1H), 7.37 (t, J = 73.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 3.6 Hz, 2.8 Hz, 1H), 6.49 (dd, J = 3.6 Hz, 0.8 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.29 – 3.23 (m, 3H), 2.94 – 2.91 (m, 1H), 2.41 – 2.32 (m, 2H), 2.07 – 2.04 (m, 1H), 1.78– 1.75 (m, 1H), 1.66 – 1.60 (m, 1H), 1.51 – 1.44 (m, 1H).
I-495	MS *m/z* 396.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 2.0 Hz, 1H), 6.85 (t, J = 3.6 Hz, 1H), 6.45 (d, J = 6.8 Hz, 1H), 6.44 (s, 1H), 6.37 (dd, J = 1.6 Hz, J = 11.2 Hz, 1H), 4.42 – 4.38 (m, 1H), 3.15 – 3.13 (m, 1H), 2.72 – 2.70 (m, 1H), 2.49 – 2.43 (m, 2H), 2.25 – 2.17 (m, 2H), 2.04 – 2.02 (m, 1H), 1.86 – 1.77 (m, 2H), 1.71 – 1.66 (m, 1H), 1.57 – 1.55 (m, 1H), 1.07 (t, J = 7.6 Hz, 3H), 0.97 – 0.92 (m, 2H), 0.68 – 0.64 (m, 2H). NH and OH not observed
I-496	MS *m/z* 343.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 7.88 (d, J= 2.0 Hz, 1H), 7.63 (t, J = 5.2 Hz, 1H), 6.88 (t, J= 3.2 Hz, 1H), 6.54(s, 1H), 6.47(d, J = 10.8 Hz, 1H), 6.33 (d, J = 4.0 Hz, 1H), 4.97 (d, J= 4.4 Hz, 1H), 4.06 – 4.02 (m, 1H), 3.58 – 3.51(m, 1H), 3.45 – 3.42(m, 1H), 1.95 – 1.89 (m, 1H), 1.15(d, J= 6.4 Hz, 3H), 1.01– 0.97 (m, 2H),0.72 – 0.69 (m, 2H).
I-497	MS *m/z* 410.2, 412.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H, formic acid proton), 8.00 (t, J= 2.5 Hz, 2H), 7.89 (dd, J= 8.3, 1.9 Hz, 1H), 7.66 (d, J= 8.3 Hz, 1H), 7.33 (s, 1H), 6.93 (t, J= 3.2 Hz,1H), 6.34 (dd, J= 3.8, 0.9 Hz,

Compound	Spectral Data
	1H), 4.31 (s, 1H), 3.09 (d, J= 7.5 Hz, 1H), 2.74 (d, J= 10.6 Hz, 1H), 2.24 (s, 3H),2.03–1.93 (m, 3H), 1.79–1.76 (m, 1H), 1.63–1.60 (m,1H), 1.45–1.41 (m,1H).
I-499	MS *m/z* 317.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.74 (d, J= 1.8 Hz, 1H), 6.93(t, J= 4.0Hz, 1H), 6.61 (s, 1H), 6.57 (dd, J= 10.6, 0.6 Hz, 1H), 6.54 –6.51 (m, 1H), 4.25–4.10(m, 1H), 3.71 (dd, J= 13.8, 4.1 Hz, 1H), 3.59 –3.48 (m, 1H), 2.34 (s, 3H), 1.27 (d, J= 6.3 Hz, 3H). NH and OH not observed.
I-500	MS *m/z* 343.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.99 (s, 1H), 7.88 (d, J= 1.2 Hz, 1H), 7.63 (t, J= 5.6 Hz, 1H), 6.88 (t, J= 3.6 Hz, 1H), 6.5 3 (s, 1H), 6.47(d, J = 10.8 Hz, 1H), 6.33 (d, J = 4.0 Hz, 1H), 4.9 6 (d, J= 4.8 Hz, 1H), 4.08 – 4.03 (m, 1H), 3.58 – 3.52 (m, 1H), 3.49 – 3.39 (m, 1H), 1.95 – 1.88(m, 1H), 1.15 (d, J= 6.0Hz, 3H), 1.01 – 0.97 (m, 2H), 0.73 – 0.69 (m, 2H).
I-502	MS *m/z* 390.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.45 (br s, 1H), 7.83 – 7.72 (m, 1H), 7.00 – 6.90 (m, 1H), 6.64 – 6.55 (m, 1H), 6.36 (s, 2H), 5.14 – 4.92 (m, 1H), 4.83 – 4.72 (m, 1H), 3.82 (s, 3H), 3.41 – 3.34 (m, 1H), 3.18 – 3.06 (m, 1H), 2.45 (m, 5H), 2.38 – 2.27 (m, 1H), 2.04–1.80 (m, 1H). NH and OH not seem
I-505	MS *m/z* 406.5, 408.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.88 (s, 1H), 7.83 (s, 1H), 7.73 – 7.61 (m, 2H), 7.00 (s, 1 H), 6.94 (d, J = 55.4 Hz, 2H), 6.60 (s, 1H), 4.58 – 4.44 (m, 1H), 3.59 – 3.42 (m, 1H), 3.16 – 2.99 (m, 1H), 2.89 – 2.72 (m, 2H), 2.70 – 2.46 (m, 2H), 2.27 – 2.12 (m, 1H), 2.05 – 1.94 (m, 1H), 1.94 – 1.65 (m, 2H), 1.33 – 1.16 (m, 3H). NH and OH not observed
I-506	MS *m/z* 422.6, 424.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.88 (s, 1H), 7.84 (s, 1H), 7.74 – 7.62 (m, 2H), 7.01 (s, 1 H), 6.98 (t, J = 55.0 Hz, 1H), 6.62 (s, 1H), 4.63 – 4.53(m, 1H), 3.92 – 3.82 (m, 2H), 3.81 – 3.71 (m, 1H), 3.44 – 3.34 (m, 1H), 3.22 – 3.06 (m, 2H), 3.06 – 2.81 (m, 2H), 2.27 – 2.17 (m, 1H), 2.17 – 2.05 (m, 1H), 2.03 – 1.75 (m, 2H). 2H not observed (NH, OH).
I-507	MS *m/z* 416.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.95 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.37 – 7.30 (m, 2H), 7.03 (t, J = 55.5 Hz, 1H), 6.96 (s, 1H), 6.51 (br s, 1H), 5.00 (d, J = 48.0 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.08 (br d, J = 8.3 Hz, 1H), 3.03 – 2.80 (m, 1H), 2.33 - 2.19 (m, 5H), 2.17 – 1.96 (m, 2H), 1.88 – 1.63 (m, 1H), 1.09 – 1.02 (m, 2H), 0.83 – 0.75 (m, 2H)
I-508	MS *m/z* 412.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.86 (s, 1H), 7.54 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.00 (s, 1H), 6.86 (t, J = 56.0 Hz, 1H), 6.60 (s, 1H), 4.63 – 4.48 (m, 1H), 3.98 – 3.76 (m, 1H), 3.60 – 3.43 (m, 1H), 3.28 – 3.19 (m, 2H), 3.14 – 2.86 (m, 2H), 2.33 – 2.15 (m, 2H), 2.14 – 2.03 (m, 1H), 2.04 – 1.80 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.9 Hz, 2H), 0.86 – 0.79 (m, 2H). 1H not observed (NH).
I-509	MS *m/z* 428.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.85 (s, 1H), 7.54 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 6.99 (s, 1 H), 6.87 (t, J = 56.3 Hz, 1H), 6.59 (s, 1H), 4.63 – 4.51 (m, 1H), 3.92 – 3.84 (m, 2H), 3.83 – 3.73 (m, 1H), 3.45 – 3.36 (m, 1H), 3.21 – 3.09 (m, 2H), 3.02 – 2.80 (m, 2H), 2.28 – 2.16 (m, 1H), 2.16 – 2.04 (m, 2H), 2.03 – 1.78 (m, 2H), 1.11 (d, J = 7.0 Hz, 2H), 0.85 – 0.78 (m, 2H). 2H not observed (NH, OH).

Compound	Spectral Data
I-510	MS *m/z* 432.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.26 (s, 1H, formic acid), 7.86 (s, 1H), 6.99 (s, 1H), 6.66 (s, 1H), 6.53 (s, 1H), 6.48 (d, J = 11.6 Hz, 1H), 6.02 (t, J = 55.9 Hz, 1H), 4.45 – 4.34 (m, 1H), 2.94 – 2.76 (m, 3H), 2.40 (t, J = 9.88 Hz, 2H), 2.17 – 2.06 (m, 1H), 1.98 – 1.52 (m, 5H), 1.04 (d, J = 7.0 Hz, 2H), 0.78 – 0.71 (m, 2H). 2H not observed (NH and OH).
I-511	MS *m/z* 406.6 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.22 (br s, 1H, formic acid), 7.95(s, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 6.73 – 6.49 (m, 2H), 6.02 (t, J = 57.7 Hz, 1H), 4.48 – 4.33 (m, 1H), 2.95 – 2.76 (m, 4H), 2.46 – 2.23 (m, 5H), 2.17 – 2.06 (m, 1H), 1.89 – 1.67 (m, 2H), 1.67 – 1.50 (m, 1H). 2Hs not observed (NH and OH).
I-513	MS *m/z* 375.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 6.92 (t, J = 3.4 Hz, 1H), 6.63 – 6.47 (m, 1H), 6.42 – 6.27 (m, 2H), 4.53 – 4.39 (m, 1H), 3.23 – 3.06 (m, 1H), 2.82 – 2.62 (m, 1H), 2.42 – 2.17 (m, 5H), 2.16 – 2.02 (m, 1H), 1.95 – 1.84 (m, 1H), 1.82 – 1.70 (m, 1H), 1.70 – 1.53 (m, 1H). 1 OH and 1 NH signals are not observed.
I-516	MS *m/z* 514.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.21 (br s, 2H), 8.00 - 7.77 (m, 2H), 7.02 (br s, 1H), 6.49 (br s, 1H), 4.72 - 4.49 (m, 1H), 4.17 - 3.80 (m, 3H), 3.56 - 3.38 (m, 4H), 3.16 - 2.90 (m, 2H), 2.17 (br s, 2H), 2.13 - 1.73 (m, 6H); NH wasn't observed
I-517	MS *m/z* 500.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ = 8.27 - 8.06 (m, 2H), 7.98 - 7.77 (m, 2H), 7.01 (br s, 1H), 6.47 (br s, 1H), 4.54 (br s, 1H), 4.09 - 3.84 (m, 3H), 3.82 - 3.71 (m, 1H), 3.68 - 3.47 (m, 2H), 3.27 - 3.05 (m, 1H), 2.85 - 2.64 (m, 2H), 2.37 - 2.17 (m, 2H), 2.17 - 1.99 (m, 2H), 1.98 - 1.71 (m, 2H); NH wasn't observed
I-519	MS *m/z* 458.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.89 – 7.79 (m, 1H), 7.72 – 7.64 (m, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.28 (m, 1H), 7.05 – 6.64 (m, 2H), 6.60 – 6.52 (m, 1H), 4.58 – 4.38 (m, 1H), 3.24 – 3.08 (m, 1H), 2.85 – 2.67 (m, 1H), 2.48 – 2.19 (m, 5H), 2.17 – 2.00 (m, 1H), 1.96 – 1.84 (m, 1H), 1.83 – 1.70 (m, 1H), 1.69 – 1.53 (m, 1H). NH peak not observed
I-520	MS *m/z* 488.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.92 – 7.82 (m, 1H), 7.73 – 7.64 (m, 1H), 7.42 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 7.06 – 6.64 (m, 2H), 6.60 – 6.51 (m, 1H), 4.56 – 4.40 (m, 1H), 3.80 – 3.64 (m, 2H), 3.24 – 3.08 (m, 1H), 2.82 – 2.53 (m, 3H), 2.53 – 2.35 (m, 2H), 2.16 – 1.97 (m, 1H), 1.95 – 1.80 (m, 1H), 1.80 – 1.59 (m, 2H). NH peak not observed
I-522	MS *m/z* 445.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.87 – 7.80 (m, 1H), 7.73 – 7.64 (m, 1H), 7.40 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 7.07 – 6.65 (m, 2H), 6.61 – 6.50 (m, 1H), 4.32 – 4.20 (m, 1H), 2.72 – 2.60 (m, 2H), 2.33 – 2.18 (m, 2H), 1.44 (s, 3H). NH and OH peak not observed
I-523	MS *m/z* 395.6 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.13 – 8.00 (m, 1H), 7.96 – 7.85 (m, 1H), 7.34 – 7.18 (m, 1H), 7.13 – 7.01 (m, 1H), 6.96 – 6.81 (m, 2H), 4.31 – 4.13 (m, 1H), 2.72 – 2.58 (m, 2H), 2.35 – 2.16 (m, 2H), 1.45 (s, 3H). NH and OH peak not observed
I-524	MS *m/z* 461.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.80 – 7.74 (m, 1H), 7.73 – 7.66 (m, 2H), 7.62 – 7.55 (m, 1H), 7.16 – 6.70 (m, 2H), 4.30 – 4.16

Compound	Spectral Data
	(m, 1H), 3.79 – 3.64 (m, 1H), 2.50 – 2.36 (m, 1H), 2.19 – 2.06 (m, 1H), 2.05 – 1.96 (m, 1H), 1.95 – 1.83 (m, 1H), 1.58 – 1.17 (m, 4H).
I-525	MS *m/z* 447.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.81 – 7.73 (m, 1H), 7.73 – 7.67 (m, 2H), 7.60 – 7.56 (m, 1H), 7.13 – 6.71 (m, 2H), 4.33 – 4.19 (m, 1H), 2.72 – 2.59 (m, 2H), 2.31 – 2.18 (m, 2H), 1.44 (s, 3H).
I-526	MS *m/z* 411.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.06 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.27 (s, 1H), 7.05 (s, 1H), 4.21 – 4.06 (m, 1H), 3.78 – 3.65 (m, 1H), 2.49 – 2.35 (m, 1H), 2.20 – 2.09 (m, 1H), 2.05 – 1.95 (m, 1H), 1.95 – 1.83 (m, 1H), 1.59 – 1.19 (m, 4H).
I-530	MS *m/z* : 472.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ : 8.16 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 6.97 – 6.95 (m, 1H), 6.41 (d, J = 3.6 Hz, 1H), 4.48 – 4.46 (m, 1H), 3.30 – 3.22 (m, 1H), 2.85 – 2.79 (m, 2H), 2.43 – 2.38 (m, 2H), 2.14 – 2.10 (m, 1H), 1.87 – 1.85 (m, 1H), 1.76 – 1.75 (m, 1H), 1.62 – 1.60 (m, 1H), 1.13 (d, J = 6.4 Hz, 6H). NH and OH not observed.
I-531	MS *m/z* : 419.2 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ : 8.17 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.90 – 7.79 (m, 2H), 7.00 (t, J = 8.0 Hz, 1H), 6.44 (d, J = 3.6 Hz, 1H), 3.73 (s, 2H), 1.32 (s, 6H). NH and OH not observed.
I-532	MS *m/z* : 431.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.16 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 6.97 – 6.95 (m, 1H), 6.41 (d, J = 2.8 Hz, 1H), 4.36 – 4.26 (m, 1H), 2.68 – 2.63 (m, 2H), 2.30 – 2.24 (m, 2H), 1.44 (s, 3H). NH and OH not observed.
I-533	MS *m/z* : 390.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 7.97 (d, J = 1.8 Hz, 1H), 7.72 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 6.0 Hz, 1H), 6.95 – 6.78 (m, 1H), 6.26 (d, J = 3.0 Hz, 1H), 4.30 (s, 1H), 3.06 (d, J = 7.2 Hz, 1H), 2.71 (d, J = 10.6 Hz, 1H), 2.22 (s, 3H), 2.02 (d, J = 8.7 Hz, 1H), 1.96 – 1.85 (m, 2H), 1.80 – 1.72 (m, 1H), 1.66 – 1.55 (m, 1H), 1.48 – 1.36 (m, 1H).
I-534	MS *m/z* : 416.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d :7.96 (d, J = 1.6 Hz, 1H), 7.65 – 7.54 (m, 1H), 7.49 – 7.36 (m, 2H), 7.20 (d, J = 7.8 Hz, 1H), 6.93 – 6.83 (m, 1H), 6.27 (d, J = 3.0 Hz, 1H), 4.37 – 4.19 (m, 1H), 3.06 (d, J = 9.8 Hz, 1H), 2.77 – 2.61 (m, 1H), 2.22 (s, 3H), 2.16 – 2.10 (m, 1H), 2.06 – 1.96 (m, 1H), 1.96 – 1.83 (m, 2H), 1.80 – 1.69 (m, 1H), 1.66 – 1.53 (m, 1H), 1.47 – 1.34 (m, 1H), 1.12 – 1.01 (m, 2H), 0.88 – 0.77 (m, 2H).
I-536	MS *m/z* : 417.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.04 (d, J = 1.8 Hz, 1H), 7.88 – 7.75 (m, 2H), 7.70 (s, 1H), 7.60 – 7.50 (m, 1H), 7.36 (t, J = 70.2 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.53 – 6.43 (m, 1H), 4.90 (s, 1H), 3.64 (d, J = 5.9 Hz, 2H), 1.21 (s, 6H). NH and OH not observed.
I-537	MS *m/z* : 429.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 7.97 (d, J = 1.8 Hz, 1H), 7.85 – 7.74 (m, 3H), 7.69 (s, 1H), 7.36 (t, J = 73.4 Hz, 1H), 7.00 – 6.92 (m, 1H), 6.48 (d, J = 3.0 Hz, 1H), 5.07 (s, 1H), 4.24 - 4.20 (m, 1H), 2.48 – 2.41 (m, 2H), 2.26 – 2.15 (m, 2H), 1.34 (s, 3H).

Compound	Spectral Data
I-539	MS *m/z* : 331.1 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.76 (d, J = 1.6 Hz, 1H), 6.95 (t, J = 3.6 Hz, 1H), 6.62 (s, 1H), 6.58 – 6.53 (m, 2H), 3.71 (s, 2H), 3.34 (s, 3H), 1.31 (s, 6H). NH and OH not observed.
I-540	MS *m/z* : 357.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.96 (s, 1H), 6.93 (d, J = 5.6 Hz, 1H), 6.60 (s, 1H), 6.44 (d, J = 12.0 Hz, 1H), 3.74 (s, 2H), 1.89 – 1.83 (m, 1H), 1.37 (s, 6H), 1.04 – 0.99 (m, 2H), 0.78 – 0.74 (m, 2H).
I-541	MS *m/z* : 410.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 7.90 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 3.2 Hz, 1H), 6.54 (s, 1H), 6.50 (d, J = 10.4 Hz, 1H), 6.32 (d, J = 4.0 Hz, 1H), 4.26 – 4.24 (m, 1H), 3.11 (d, J = 7.6 Hz, 1H), 2.80 – 2.74 (m, 2H), 2.13 (t, J = 10.4 Hz, 2H), 2.06 – 2.03 (m, 1H), 1.94 – 1.90 (m, 1H), 1.77 – 1.74 (m, 1H), 1.56 – 1.40 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H), 1.00 – 0.92 (m, 2H), 0.73 – 0.69 (m, 2H).
I-542	MS *m/z* : 450.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d : 7.88 (d, J = 1.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 3.2 Hz, 1H), 6.54 (s, 1H), 6.47 (d, J = 11.2 Hz, 1H), 6.33 (d, J = 3.6 Hz, 1H), 4.31 – 4.23 (m, 1H), 3.29 – 3.10 (m, 3H), 2.94 – 2.88 (m, 1H), 2.37 (t, J = 10.4 Hz, 2H), 2.06 – 2.03 (m, 1H), 1.95 – 1.87 (m, 1H), 1.78 – 1.75 (m, 1H), 1.65 – 1.54 (m, 1H), 1.50 – 1.40 (m, 1H), 1.01 – 0.93 (m, 2H), 0.73 – 0.67 (m, 2H).
I-552	MS *m/z* 446.4, 448.4 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 8.17 (s, 1H, formic acid proton), 8.11 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.19 (d, J = 9.7 Hz, 2H), 7.13 (d, J = 8.3 Hz, 1H), 7.08 (s, 1H), 4.26-4.30 (m, 1H), 3.42-3.48 (m, 2H), 3.17 – 3.02 (m, 2H), 2.70-2.78 (m, 2H), 2.47 – 2.20 (m, 2H), 1.96-2.02 (m, 1H), 1.72-1.80 (m, 1H), 1.44-1.60 (m, 2H), 0.95 (d, J = 6.3 Hz, 3H). NH peak not observed
I-562	MS *m/z* 359.5 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.83 (s, 1H), 6.96 (m, 1H), 6.63 (m, 1H), 6.37 (m, 2H), 4.24 (t, J = 7.8 Hz, 1H), 3.82 (s, 3H), 2.74 – 2.54 (m, 2H), 2.26 (t, J = 9.8 Hz, 2H), 1.44 (m, 3H). NH and OH peak not observed
I-563	MS *m/z* 370.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.43 (s, 1H, formic acid), 7.81 (s, 1H), 6.97 (s, 1H), 6.66 (s, 1H), 6.62 (d, J = 10.4 Hz, 1H), 6.58 (s, 1H), 4.61 – 4.52 (m, 1H), 3.85 – 3.71 (m, 1H), 3.38 – 3.33 (m, 1H), 3.10 – 2.90 (m, 2H), 2.84 (s, 3H), 2.66 (q, J = 7.3 Hz, 2H), 2.28 – 2.19 (m, 1H), 2.18 – 2.10 (m, 1H), 2.01 – 1.80 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H). 2H not observed (NH and OH).
I-565	MS *m/z* 472.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.88 – 7.80 (m, 1H), 7.70 – 7.65 (m, 1H), 7.39 – 7.29 (m, 2H), 7.06 – 6.64 (m, 2H), 6.59 – 6.52 (m, 1H), 4.58 – 4.41 (m, 1H), 3.31 – 3.19 (m, 1H), 2.94 – 2.77 (m, 1H), 2.69 – 2.50 (m, 2H), 2.41 – 2.22 (m, 2H), 2.21 – 2.05 (m, 1H), 1.98 – 1.83 (m, 1H), 1.84 – 1.55 (m, 2H), 1.22 – 1.10 (m, 3H). NH peak not observed.
I-566	MS *m/z* 474.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.81 – 7.74 (m, 1H), 7.73 – 7.67 (m, 2H), 7.61 – 7.55 (m, 1H), 7.13 – 6.72 (m, 2H), 4.55 – 4.40 (m, 1H), 3.28 – 3.16 (m, 1H), 2.89 – 2.74 (m, 1H), 2.63 – 2.44 (m, 2H), 2.37 – 2.18 (m, 2H), 2.16 – 2.03 (m, 1H), 1.94 – 1.83 (m, 1H), 1.82 – 1.55 (m, 2H), 1.21 – 1.10 (m, 3H). NH peak not observed.

Compound	Spectral Data
I-568	MS *m/z* 431.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6)δ 8.08 (d, J = 1.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.43 (t, J = 6.0 Hz, 1H), 7.27 (t, J = 73.4 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.49 (d, J = 3.1 Hz, 1H), 3.74 (d, J = 5.9 Hz, 2H), 3.20 (s, 3H), 1.22 (s, 6H).
I-569	MS *m/z* 384.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ : 9.93 (s, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.95 – 6.81 (m, 1H), 6.62 (s, 1H), 6.60 (d, J = 10.8 Hz, 1H), 6.31 (d, J = 3.8 Hz, 1H), 4.24 (br s, 1H), 3.11 (d, J = 7.0 Hz, 1H), 2.83 – 2.71 (m, 2H), 2.30 (s, 3H), 2.13 (t, J = 10.1 Hz, 2H), 2.07 – 1.97 (m, 1H), 1.81 – 1.70 (m, 1H), 1.62 – 1.49 (m, 1H), 1.47 – 1.30 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H).
I-570	MS *m/z* 424.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d : 9.92 (s, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 6.92 – 6.85 (m, 1H), 6.62 (s, 1H), 6.60 (d, J = 10.6 Hz, 1H), 6.31 (d, J = 3.8 Hz, 1H), 4.29 (br s, 1H), 3.31 – 3.20 (m, 3H), 2.93 (d, J = 10.8 Hz, 1H), 2.37 (t, J = 10.4 Hz, 2H), 2.30 (s, 3H), 2.04 (d, J = 9.2 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.67 – 1.54 (m, 1H), 1.52 – 1.38 (m, 1H).
I-573	MS *m/z* 427.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d : 7.94 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.40 (t, J =73.2 Hz, 1H), 7.25 (t, J =73.6 Hz, 1H), 7.22 (d, J = 3.2 Hz, 1H), 7.22 (d, J = 2 Hz, 1H), 6.93 (t, J = 3.6 Hz, 1H), 6.42 (t, J = 2.8 Hz, 1H), 5.02 (s, 1H), 4.24 - 4.18 (m,1H), 2.51 - 2.49 (m, 2H), 2.22 - 2.17 (m, 2H), 1.33 (s, 3H).
I-575	MS *m/z* 396.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.04 (d, J = 8.0Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.16 (dt, J = 6.8, 3.6 Hz, 2H), 5.62 – 5.33 (m, 1H), 4.33 – 4.22 (m, 1H), 4.14 (dd, J = 15.0, 2.8 Hz, 1H), 3.99 (dd, J = 15.0, 7.0 Hz, 1H), 3.72 – 3.51 (m, 2H), 2.63 – 2.51 (m, 1H), 2.35 – 2.11 (m, 1H). NH peak not observed.
I-576	MS *m/z* 414.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) d : 9.93 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.54 (s, 1H), 6.48 (d, J = 11.0 Hz, 1H), 6.34 (d, J = 3.7 Hz, 1H), 5.01 (d, J = 47.6 Hz, 1H), 4.59 (br s, 1H), 3.17 (d, J = 9.8 Hz, 1H), 3.03 (t, J = 10.8 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.35 – 2.27 (m, 1H), 2.27 – 2.12 (m, 1H), 2.05 (t, J = 10.1 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.89 – 1.67 (m, 1H), 1.02 (t, J = 7.2 Hz, 3H), 1.00 – 0.96 (m, 2H), 0.77 – 0.67 (m, 2H).
I-577	MS *m/z* 337.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.65 (d, J = 2.0 Hz, 1H), 6.85 (t, J = 3.2 Hz, 1H), 6.69 – 6.67 (m, 2H), 6.43 (d, J = 3.6 Hz, 1H), 4.07 – 4.09 (m, 1H), 3.59 – 3.64 (m, 1H), 3.41 – 3.47 (m, 1H), 1.17 (d, J = 6.4 Hz, 3H). NH peak not observed.
I-582	MS *m/z* 370.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.53 (s, 1H, formic acid), 7.76 (s, 1H), 7.02 (s, 1H), 6.68 – 6.55 (m, 3H), 4.13 (d, J = 14.9 Hz, 1H), 3.92 – 3.78 (m, 2H), 3.72 – 3.48 (m, 2H), 3.26 – 3.10 (m, 2H), 2.36 (s, 3H), 2.33 – 2.25 (m, 1H), 2.19 – 1.92 (m, 3H), 1.44 (t, J = 7.2 Hz, 3H). 2H not observed (NH and OH).
I-583	MS *m/z* 396.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.45 (s, 1 H, formic acid), 7.76 (s, 1H), 7.02 (s, 1H), 6.62 (s, 1H), 6.54 (s, 1H), 6.48 (d, J = 10.6 Hz, 1H), 4.15 (d, J = 14.1 Hz, 1H), 3.92 – 3.81 (m, 2H), 3.74 – 3.57 (m,

Compound	Spectral Data
	2H), 3.28 – 3.17 (m, 2H), 2.37 – 2.24 (m, 1H), 2.19 – 1.86 (m, 4H), 1.44 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 7.0 Hz, 2H), 0.80 – 0.69 (m, 2H). 2H not observed (NH and OH). NH peak not observed.
I-586	MS *m/z* 325.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.87 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.23 (d, J = 2.6 Hz, 1H), 7.04 (s, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.69 (s, 1H), 4.23 – 4.12 (m, 1H), 3.73 – 3.64 (m, 1H), 3.55 – 3.44 (m, 1H), 1.98 – 1.86 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H), 1.05 – 0.95 (m, 2H), 0.81 – 0.71 (m, 2H). 3H not observed (NH and 2 OH).
I-587	MS *m/z* 315.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.94 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 6.58 (d, J = 10.0 Hz, 1H), 6.53 (s, 1H), 4.22 – 4.11 (m, 1H), 3.83 (s, 3H), 3.71 – 3.63 (m, 1H), 3.53 – 3.44 (m, 1H), 1.27 (d, J = 6.1 Hz, 3H). 3H not observed (NH and 2 OH).
I-588	MS *m/z* 353.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.15 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.30 – 7.22 (m, 3H), 7.09 (s, 1H), 4.23 – 4.13 (m, 1H), 3.78 – 3.66 (m, 1H), 3.58 – 3.46 (m, 1H), 1.28 (d, J = 6.1 Hz, 3H). 3H not observed (NH and 2 OH).
I-589	MS *m/z* 431.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.17 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.80 (s, 1H), 6.98 (bs, 1H), 6.43 (s, 1H), 3.99 – 3.86 (m, 2H), 3.83 – 3.75 (m, 1H), 3.75 – 3.59 (m, 3H), 2.94 – 2.81 (m, 1H), 2.22 – 2.09 (m, 1H), 1.87 – 1.74 (m, 1H). 1H not observed (NH).
I-590	MS *m/z* 431.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.17 (s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.80 (s, 1H), 6.98 (s, 1H), 6.43 (s, 1H), 4.00 – 3.85 (m, 2H), 3.85 – 3.74 (m, 1H), 3.74 – 3.60 (m, 3H), 2.94 – 2.80 (m, 1H), 2.23 – 2.08 (m, 1H), 1.88 – 1.72 (m, 1H). 1H not observed (NH).
I-591	MS *m/z* 456.4 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.84 – 7.69 (m, 2H), 7.63 (m, 2H), 7.13 – 6.67 (m, 1H), 6.39 (s, 1H), 4.54 – 4.41 (m, 1H), 2.93 – 2.82 (m, 1H), 2.47 (m, 5H), 2.33 (s, 3H), 2.19 (s, 1H), 2.17 – 2.06 (m, 1H), 1.99 – 1.88 (m, 1H), 1.85 – 1.73 (m, 1H), 1.73 – 1.58 (m, 1H). NH peak was not observed
I-592	MS *m/z* 488.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.81 – 7.66 (m, 3H), 7.62 – 7.56 (m, 1H), 7.14 – 6.72 (m, 2H), 4.57 – 4.40 (m, 1H), 3.48 – 3.35 (m, 1H), 3.11 – 2.92 (m, 2H), 2.67 – 2.44 (m, 2H), 2.27 – 2.08 (m, 1H), 2.04 – 1.89 (m, 1H), 1.87 – 1.57 (m, 2H), 1.20 (s, 6H). NH peak not observed
I-593	MS *m/z* 397.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.88 – 7.53 (m, 2H), 7.34 – 7.07 (m, 2H), 6.93 – 6.73 (m, 1H), 4.35 – 4.08 (m, 1H), 2.77 – 2.53 (m, 2H), 2.39 – 2.13 (m, 2H), 1.43 (s, 3H). NH and OH peak not observed
I-594	MS *m/z* 424.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 1H, formic acid proton), 7.77 – 7.69 (m, 1H), 7.68 – 7.59 (m, 1H), 7.29 – 7.14 (m, 2H), 6.91 – 6.76 (m, 1H), 4.58 – 4.42 (m, 1H), 3.67 – 3.51 (m, 1H), 3.24 – 3.12 (m, 1H), 2.99 – 2.83 (m, 2H), 2.77 – 2.52 (m, 2H), 2.27 – 2.13 (m, 1H), 2.11 – 1.97 (m, 1H), 1.95 – 1.64 (m, 2H), 1.38 – 1.19 (m, 3H). NH and OH peak not observed

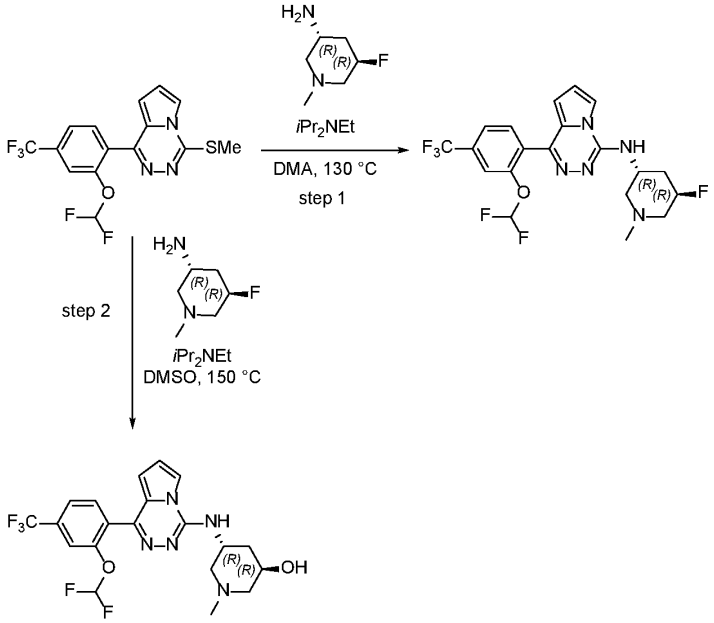
Compound	Spectral Data
I-595	MS *m/z* 371.3 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d4) δ 7.81 – 7.55 (m, 2H), 7.30 – 7.13 (m, 2H), 6.94 – 6.75 (m, 1H), 4.27 – 4.07 (m, 1H), 3.79 – 3.61 (m, 1H), 3.58 – 3.45 (m, 1H), 1.35 – 1.21 (m, 3H). NH and OH peak not observed
I-599	MS *m/z* 382.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.77 – 7.65 (m, 1H), 7.48 – 7.38 (m, 1H), 6.85 – 6.77 (m, 1H), 6.72 – 6.62 (m, 2H), 4.47 – 4.32 (m, 1H), 3.23 – 3.10 (m, 1H), 2.90 – 2.69 (m, 1H), 2.51 – 2.27 (m, 5H), 2.18 – 2.00 (m, 1H), 1.98 – 1.84 (m, 2H), 1.83 – 1.56 (m, 2H), 1.06 – 0.94 (m, 2H), 0.81 – 0.68 (m, 2H). NH and OH peak not observed
I-600	MS *m/z* 396.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.75 – 7.65 (m, 1H), 7.47 – 7.38 (m, 1H), 6.86 – 6.77 (m, 1H), 6.72 – 6.61 (m, 2H), 4.52 – 4.33 (m, 1H), 3.43 – 3.31 (m, 1H), 3.04 – 2.85 (m, 1H), 2.79 – 2.60 (m, 2H), 2.53 – 2.33 (m, 2H), 2.22 – 2.06 (m, 1H), 2.00 – 1.87 (m, 2H), 1.84 – 1.59 (m, 2H), 1.25 – 1.15 (m, 3H), 1.06 – 0.95 (m, 2H), 0.79 – 0.67 (m, 2H). NH and OH peak not observed
I-601	MS *m/z* 400.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.70 – 7.58 (m, 1H), 6.78 – 6.68 (m, 1H), 6.51 – 6.46 (m, 1H), 6.45 – 6.38 (m, 1H), 4.54 – 4.35 (m, 1H), 3.31 – 3.17 (m, 1H), 2.94 – 2.75 (m, 1H), 2.57 – 2.30 (m, 5H), 2.18 – 2.03 (m, 1H), 2.00 – 1.86 (m, 2H), 1.84 – 1.56 (m, 2H), 1.08 – 0.95 (m, 2H), 0.79 – 0.67 (m, 2H). NH and OH peak not observed
I-602	MS *m/z* 414.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.71 – 7.57 (m, 1H), 6.79 – 6.69 (m, 1H), 6.52 – 6.46 (m, 1H), 6.45 – 6.38 (m, 1H), 4.53 – 4.39 (m, 1H), 3.48 – 3.35 (m, 1H), 3.05 – 2.91 (m, 1H), 2.81 – 2.63 (m, 2H), 2.56 – 2.33 (m, 2H), 2.21 – 2.06 (m, 1H), 2.02 – 1.59 (m, 4H), 1.26 – 1.16 (m, 3H), 1.09 – 0.95 (m, 2H), 0.79 – 0.67 (m, 2H). NH and OH peak not observed
I-604	MS *m/z* 440.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.78 – 7.66 (m, 1H), 7.63 – 7.51 (m, 1H), 6.92 – 6.75 (m, 3H), 4.56 – 4.38 (m, 1H), 3.61 – 3.44 (m, 1H), 3.19 – 3.02 (m, 1H), 2.93 – 2.74 (m, 2H), 2.71 – 2.48 (m, 2H), 2.25 – 2.11 (m, 1H), 2.08 – 1.94 (m, 1H), 1.92 – 1.65 (m, 2H), 1.33 – 1.16 (m, 3H). NH and OH peak not observed
I-606	MS *m/z* 420.2 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.01 - 7.77 (m, 1H), 7.25 - 6.87 (m, 3H), 6.49 (br s, 1H), 4.74 - 4.53 (m, 1H), 4.06 - 3.80 (m, 1H), 3.61 - 3.41 (m, 1H), 3.30 - 3.19 (m, 2H), 3.15 - 2.97 (m, 2H), 2.35 - 2.07 (m, 5H), 2.07 - 1.85 (m, 2H), 1.39 (br s, 3H); 2H (NH and OH) wasn't observed
I-607	MS *m/z* 424.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.25 (br s, 1H), 7.82 – 7.66 (m, 1H), 7.19 (d, J = 9.1 Hz, 1H), 7.14 – 7.11 (m, 1H), 7.13 – 7.07 (m, 1H), 6.20 (s, 1H), 4.27 (m, 1H), 3.05 (m, 1H), 2.75 – 2.64 (m, 1H), 2.22 (m, 6H), 2.03 – 1.84 (m, 3H), 1.76 (m, 1H), 1.67 – 1.51 (m, 1H), 1.49 – 1.34 (m, 1H). OH peak not observed.
I-608	MS *m/z* 363.1, 365.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.35 (d, J = 2.4 Hz, 1H),7.00 (t, J= 3.6Hz, 1H), 6.90 – 6.92 (m, 2H), 6.77 (dd, J = 2.0Hz,10.8 Hz,1H), 5.31 – 5.34 (m, 1H), 4.49 – 4.51 (m, 1H),3.89 – 3.94 (m, 2H),3.67 (dd, J= 3.2 Hz, 12 Hz, 1H), 2.14 – 2.22 (m, 1H), 1.98 – 2.03 (m, 1H), 1.62 – 1.65 (m, 1H). NH and OH not observed

Compound	Spectral Data
I-609	MS *m/z* 422.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.12 – 8.05 (m, 2H), 7.48 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 3.7 Hz, 1H), 7.12 – 7.07 (m, 1H), 6.95 – 6.88 (m, 2H), 4.27 (br s, 1H), 3.16 (d, J = 6.9 Hz, 1H), 2.83 (d, J = 10.7 Hz, 1H), 2.39 (q, J = 7.2 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.99 – 1.86 (m, 2H), 1.84 – 1.73 (m, 1H), 1.70 – 1.53 (m, 1H), 1.52 – 1.43 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H). one proton is overlapped with d-solvent peak
I-610	MS *m/z* : 429.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 7.96 (d, J = 1.9 Hz, 1H), 7.88 (t, J = 5.5 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.70 (s, 1H), 7.36 (t, J = 73.4 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.49 (d, J = 3.8 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.84 (dd, J = 14.2, 7.2 Hz, 1H), 3.74 – 3.54 (m, 3H), 2.01 (td, J = 12.4, 7.3 Hz, 1H), 1.95 – 1.81 (m, 2H), 1.73 – 1.60 (m, 1H).
I-611	MS *m/z* : 429.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) δ 7.96 (dd, J = 2.8, 1.1 Hz, 1H), 7.88 (t, J = 5.5 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.70 (s, 1H), 7.36 (t, J = 73.4 Hz, 1H), 6.96 (dd, J = 3.8, 2.9 Hz, 1H), 6.49 (dd, J = 3.9, 1.1 Hz, 1H), 4.36 – 4.14 (m, 1H), 3.89 – 3.78 (m, 1H), 3.75 – 3.56 (m, 3H), 2.07 – 1.95 (m, 1H), 1.92 – 1.81 (m, 2H), 1.71 – 1.62 (m, 1H).
I-612	MS *m/z* 440.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.96 (d, J = 2.1 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 73.2 Hz, 1H), 7.25 – 7.16 (m, 4H), 6.96 – 6.91 (m, 1H), 6.43 (d, J = 3.8 Hz, 1H), 4.43 – 4.21 (m, 1H), 3.12 – 3.06 (m, 1H), 2.76 – 2.63 (m, 1H), 2.21 (s, 3H), 2.07 – 1.99 (m, 1H), 1.97 – 1.86 (m, 2H), 1.82 – 1.72 (m, 1H), 1.68 – 1.56 (m, 1H), 1.47 – 1.35 (m, 1H).
I-613	MS *m/z* 454.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.95 (d, J = 1.9 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 15.2 Hz, 1H), 7.32 – 7.12 (m, 4H), 6.97 – 6.88 (m, 1H), 6.43 (d, J = 3.2 Hz, 1H), 4.37 – 4.21 (m, 1H), 3.17 (d, J = 7.0 Hz, 1H), 2.83 (d, J = 10.3 Hz, 1H), 2.39 (q, J = 7.1 Hz, 2H), 2.08 – 2.01 (m, 1H), 1.96 – 1.86 (m, 2H), 1.82 – 1.72 (m, 1H), 1.69 – 1.54 (m, 1H), 1.50 – 1.40 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H).
I-614	MS *m/z* 470.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.97 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.48 – 7.36 (m, 1H), 7.28 – 7.16 (m, 4H), 6.95 - 6.93 (m, 1H), 6.46 (d, J = 3.2 Hz, 1H)., 3.78 – 3.53 (m, 3H), 3.13 – 2.74 (m, 1H), 2.21 – 1.94 (m, 3H), 1.88 – 1.39 (m, 4H), 1.20 – 0.91 (m, 2H).
I-616	MS *m/z* : 422.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.79 (dd, J = 2.8, 1.1 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.85 (t, J = 73.2 Hz, 1H), 6.61 – 6.49 (m, 3H), 4.59 – 4.38 (m, 1H), 3.27 – 3.18 (m, 1H), 2.87 – 2.73 (m, 1H), 2.61 – 2.48 (m, 2H), 2.38 – 2.22 (m, 2H), 2.17 – 2.05 (m, 1H), 1.94 – 1.84 (m, 1H), 1.84 – 1.57 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H). NH and OH not observed.
I-618	MS *m/z* : 395.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.79 (dd, J = 2.8, 1.1 Hz, 1H), 6.95 – 6.91 (m, 1H), 6.81 (t, J = 73.6 Hz, 1H), 6.56 – 6.49 (m, 3H), 4.38 – 4.17 (m, 1H), 2.72 – 2.60 (m, 2H), 2.34 – 2.18 (m, 2H), 1.43 (s, 3H). NH and OH not observed
I-621	MS *m/z* : 463.1, 365.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 7.33 (d, J= 2.0Hz, 1H), 6.95–6.97 (m, 1H), 6.88 –6.91 (m, 2H), 6.77 (dd, J= 2.0Hz, 10.8Hz, 1H),4.10(s,1H), 4.28–4.29(m, 1H),4.05 –4.09 (m, 1H), 3.87 –3.97 (m, 1H),3.81 –3.87 (m, 1H), 3.50 –3.56 (m, 1H), 2.10–2.17(m, 1H), 1.95–2.02(m, 2H). NH and OH not observed

Compound	Spectral Data
I-629	MS *m/z* 373.2 $[M+H]^+$; ^1H NMR(400 MHz, CD_3OD) δ 7.77 (d,J = 1.8 Hz, 1H), 6.94 – 6.90 (m, 1H), 6.56 (s, 1H), 6.33 (dd,J = 10.3, 2.1 Hz, 2H), 4.23 (dd,J = 16.1, 7.9 Hz, 1H), 4.05 (q,J = 7.0 Hz, 2H), 2.69 – 2.61 (m, 2H), 2.25 (t,J = 10.2 Hz, 2H), 1.41 – 1.28 (m, 6H). NH and OH not observed
I-630	MS *m/z* 386.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.78 (dd,J = 2.9, 1.1 Hz, 1H), 6.99 – 6.80 (m, 1H), 6.64 – 6.49 (m, 1H), 6.40 – 6.24 (m, 2H), 4.53 – 4.37 (m, 1H), 4.05 (q,J = 7.0 Hz, 2H), 3.13 (s, 1H), 2.71 (s, 1H), 2.35 (s, 3H), 2.30 (s, 2H), 2.06 (s, 1H), 1.87 (dd,J = 11.4, 6.6 Hz, 1H), 1.75 (dd,J = 9.9, 3.8 Hz, 1H), 1.63 (s, 1H), 1.40 (t,J = 7.0 Hz, 3H). NH and OH not observed
I-636	MS *m/z* 366.3 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.01 - 7.86 (m, 1H), 7.02 (br s, 1H), 6.78 - 6.64 (m, 2H), 6.58 (br s, 1H), 4.88 - 4.65 (m, 1H), 4.16 - 3.89 (m, 1H), 3.28 - 2.85 (m, 5H), 2.38-2.30 (m, 4H), 2.18 - 1.88 (m, 6H), 1.34 - 1.30 (m, 3H); 2H (NH and OH) wasn't observed

Example 41a

Preparation of Compounds I-413 and I-385



Step 1: 1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]-*N*-[(3*R*,5*R*)-5-fluoro-1-methyl-3-piperidyl]pyrrolo[1,2-*d*][1,2,4]triazin-4-amine

A mixture of 1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (prepared as Example 32, step 1-2, 0.070 g, 0.19 mmol) and (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-amine dihydrochloride (0.077 g, 0.37 mmol) in DMA

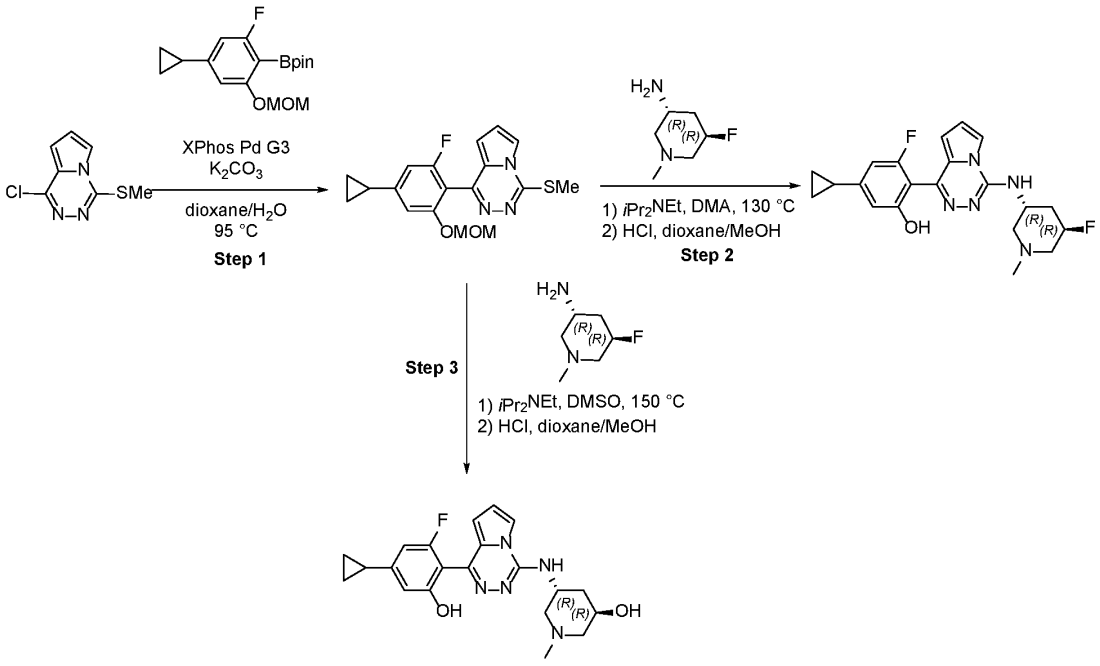
(0.19 mL) and *i*Pr$_2$NEt (0.20 mL, 1.2 mmol) was heated to 130 °C for 8 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.037 g, 43%). MS *m/z* 460.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.80 (q, *J* = 7.9 Hz, 2H), 7.70 (s, 1H), 7.41 (t, *J* = 61.2 Hz, 1H), 7.38 (s, 1 H), 6.97 (s, 1H), 6.50 (s, 1H), 5.00 (d, *J* = 45.28 Hz, 1H), 4.69 – 4.56 (m, 1H), 3.13 – 3.03 (m, 1H), 3.00 – 2.87 (m, 1H), 2.35 – 2.11 (m, 5H), 2.09 – 1.98 (m, 1H), 1.89 – 1.66 (m, 1H).

Step 2. (3R,5R)-5-[[1-[2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino]-1-methyl-piperidin-3-ol

A mixture of 1-[4-cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (prepared as Example 32, step 1-2, 0.070 g, 0.19 mmol) and (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-amine dihydrochloride (0.096 g, 0.47 mmol) in DMSO (0.31 mL) and *i*Pr$_2$NEt (0.13 mL, 0.75 mmol) was heated to 150 °C for 17 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with water, brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.026 g, 30%). MS *m/z* 440.4 $[M-H_2O+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 7.89 – 7.71 (m, 2H), 7.67 (s, 1H), 6.99 (t, *J* = 73.0 Hz, 1H), 6.91 (s, 1 H), 6.67 (s, 1H), 4.64 (br s, 1H), 4.09 (br s, 1H), 3.42 (d, *J* = 12.26 Hz, 1H), 3.26 (d, *J* = 12.63 Hz, 1H), 2.82 – 2.70 (m, 2H), 2.45 (s, 3H), 2.36 – 2.17 (m, 2H); 2Hs not observed (NH and OH).

Example 41b

Preparation of Compounds I-445 and I-387



Step 1: 1-[4-Cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine

1-Chloro-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (Intermediate 2d, 0.500 g, 2.50 mmol), 2-[4-cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (prepared according to the procedure of Intermediate 5d, 1.21 g, 3.76 mmol), and XPhos Pd G3 (0.216 g, 0.250 mmol) were placed in a vial and evacuated and refilled with Ar. Dioxane (12.5 mL) and aq. K_2CO_3 (2M, 0.3.8 mL, 7.51 mmol) were added and the solution was sparged with Ar for 5 min. The reaction was heated to 95 °C for 15 h. The reaction was cooled to rt and diluted with EtOAc. The solution was washed with water and brine. The organic phase was dried (Mg_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 0 to 60%) gave a tan solid (0.36 g, 40%). MS *m/z* 360.1 $[M+H]^+$.

Step 2. 5-Cyclopropyl-3-fluoro-2-[4-[[(3*R*,5*R*)-5-fluoro-1-methyl-3-piperidyl]amino]-pyrrolo[1,2-*d*][1,2,4]triazin-1-yl]phenol

A mixture of 1-[4-cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.070 g, 0.19 mmol) and (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-

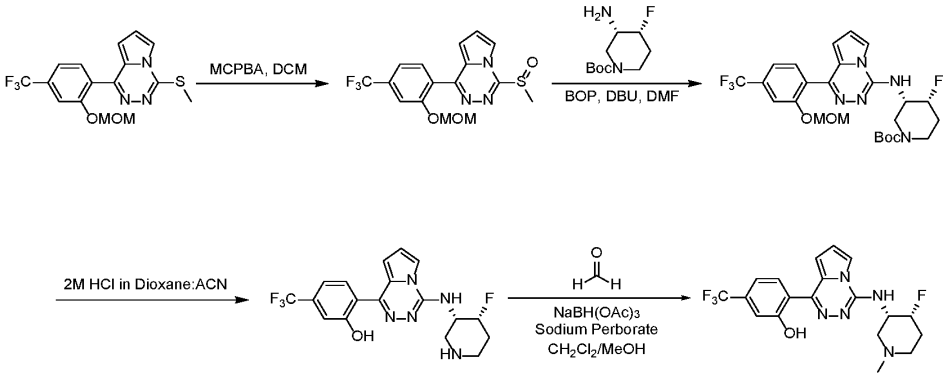
amine dihydrochloride (0.080 g, 0.39 mmol) in DMA (0.19 mL) and *i*Pr$_2$NEt (0.20 mL, 1.2 mmol) was heated to 130 °C for 8 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was dissolved in MeOH (0.5 mL) and added HCl/dioxane (4M, 1.0 mL). The reaction was stirred for 1 h. The mixture was concentrated, and the resulting residue was dissolved in DCM/iPrOH (9:1). The solution was washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.010 g, 13%). MS *m/z* 400.6 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.25 (d, *J* = 6.8 Hz, 1H), 6.89 (s, 1H), 6.54 (s, 1H), 6.47 (d, *J* = 10.8 Hz, 1H), 6.33 (s, 1H), 5.01 (d, *J* = 47.0 Hz, 1H), 4.66 – 4.53 (m, 1H), 3.08 (d, *J* = 8.8 Hz, 1H), 2.93 (t, *J* = 11.2 Hz, 1H), 2.34– 2.11 (m, 5H), 2.08 – 1.98 (m, 1H), 1.97 – 1.87 (m, 1H), 1.87 – 1.65 (m, 1H), 1.03 – 0.99 (m, 2H), 0.76 – 0.66 (m, 2H). 1H not observed (OH).

Step 3: (3*R*,5*R*)-5-[[1-(4-Cyclopropyl-2-fluoro-6-hydroxy-phenyl)pyrrolo[1,2-*d*][1,2,4]triazin-4-yl]amino]-1-methyl-piperidin-3-ol formic acid salt

A mixture of 1-[4-cyclopropyl-2-fluoro-6-(methoxymethoxy)phenyl]-4-methylsulfanyl-pyrrolo[1,2-*d*][1,2,4]triazine (0.119 g, 0.331 mmol) and (3*R*,5*R*)-5-fluoro-1-methyl-piperidin-3-amine dihydrochloride (0.153 g, 0.745 mmol) in DMSO (0.47 mL) and *i*Pr$_2$NEt (0.23 mL, 1.32 mmol) was heated to 150 °C for 12 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was dissolved in MeOH (0.5 mL) and added HCl/dioxane (4M, 1.0 mL). The reaction was stirred for 1 h. The mixture was concentrated, and the resulting residue was dissolved in DCM/iPrOH (9:1). The solution was washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a white solid (0.012 g, 8%). MS *m/z* 380.5 $[M-H_2O+H]^+$; ^{1}H NMR (500 MHz, CD_3OD) δ 8.49 (br s, 1H, formic acid), 7.81 (s, 1H), 6.83 – 6.76 (m, 1H), 6.55 – 6.43 (m, 3H), 4.53 4.47 (m, 1H), 4.00 - 3.94 (m, 1H), 3.29 (d, *J* = 11.7 Hz, 1H), 3.15 (d, *J* = 11.1 Hz, 1H), 2.60 – 2.47 (m, 2H), 2.34 (s, 3H), 2.24 – 2.09 (m, 2H), 1.97 – 1.86 (m, 1H), 1.11 – 0.99 (m, 2H), 0.78 - 0.71 (m, 2H); 3Hs not observed (2 OH, NH).

Example 42

Preparation of Compound I-486



Step 1. 1-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-4-(methylsulfinyl)pyrrolo[1,2-*d*][1,2,4]triazine

mCPBA (70%, 111 mg, 0.450 mmol, 1.5 eq) was added to a mixture of 1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4-(methylthio)pyrrolo[1,2-*d*][1,2,4]triazine (111 mg, 0.300 mmol, 1 eq., prepared in a manner analogous to Example 38, step 1, using intermediate 5a in place of 2-[2-fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane) in DCM at 0 °C. The reaction mixture was allowed to slowly return to room temperature and stirred for 30 min. After 30 min, the reaction mixture was diluted with a small amount of $NaHCO_3$ (sat. aq.), extracted several times with DCM and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was used without further purification. MS *m/z* 386.4 $[M+H]^+$.

Step 2. *tert*-Butyl (3*S*,4*R*)-4-fluoro-3-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrrolo[1,2-*d*][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate

N,N-diisopropylethylamine (0.235 mL, 1.35 mmol, 4.5 eq) was added to a solution of 1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4-(methylsulfinyl)pyrrolo[1,2-d][1,2,4]triazine (116 mg, 0.300 mmol, 1 eq) and tert-butyl (3S,4R)-3-amino-4-fluoropiperidine-1-carboxylate (131 mg, 0.600 mmol, 2 eq) in DMA (0.6 mL) and stirred at 50 0C for 1 day. The reaction mixture was allowed to slowly return to room temperature and stirred for 30 min. After completion, the reaction was diluted with EtOAc and NaHCO3 (sat. aq.). The product was extracted several times with EtOAc and the combined organic extracts were dried over Na2SO3 and concentrated in vacuo. The crude residue was purified by silica gel column chromatography

eluting with 1:100 to 20:80 MeOH:DCM to afford tert-butyl (3S,4R)-4-fluoro-3-((1-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate as an impure oil which was used without further purification. MS m/z 540.6 $[M+H]^+$.

Step 3. 2-(4-(((3*S*,4*R*)-4-Fluoropiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formic acid salt

The mixture from step 2 was suspended in ACN (2 mL) and 4 M HCl in Dioxane (1 mL) and stirred at room temperature for 2 h. Upon reaction completion solvents were removed *in vacuo*. The residue was concentrated several times from dichloromethane to remove excess HCl. The combined organic extracts were dried over sodium sulfate and the crude material was purified by flash column chromatography 0:100 to 10:90 (10% NH4OH in MeOH):DCM to afford 2-(4-(((3*S*,4*R*)-4-fluoropiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol followed by C18 reverse phase Prep-HPLC eluting with ACN:Water with formic acid as the modifier. (35 mg, 30% over three steps). MS *m/z* 396.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d_4) δ 8.47 (s, 1H), 7.91 – 7.78 (m, 1H), 7.56 – 7.29 (m, 4H), 5.43 – 5.19 (m, 1H), 5.01 – 4.87 (m, 1H), 3.78 – 3.63 (m, 1H), 3.55 – 3.36 (m, 2H), 3.32 – 3.20 (m, 1H), 2.54 – 2.40 (m, 1H), 2.38 – 2.14 (m, 1H), 3 exchangeable protons not observed.

Step 4. 2-(4-(((3*S*,4*R*)-4-Fluoro-1-methylpiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

A mixture of 2-(4-(((3*S*,4*R*)-4-fluoropiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol (33 mg, 0.083 mmol, 1 eq) and sodium perborate tetrahydrate (39 mg, 0.25o mmol, 3 eq) in DCM (1 mL) and methanol (200 µL) was stirred for 30 min at 0 °C. After 30 min, formaldehyde (37 wt% in water) (18.6 µL, 0.250 mmol, 3 eq) followed by sodium triacetoxyborohydride (53 mg, 0.250 mmol, 3 eq). The reaction was stirred at 0 °C for 1 min. The ice bath was removed, and the reaction mixture was stirred for 2 min. The reaction was quenched by addition a small amount of $NaHCO_3$ (sat, aq) and a small amount of water followed by extraction with DCM. The combined organic extracts were dried over sodium sulfate and the crude material was purified by C18 reverse phase Prep-HPLC eluting with ACN:Water with formic acid as the modifier. After reverse phase purification, solvents were removed to afford 2-(4-(((3*S*,4*R*)-4-fluoro-1-methylpiperidin-3-yl)amino)pyrrolo[1,2-*d*][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol (17.6 mg, 52%). MS *m/z* 410.5 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-

d_4) δ 8.21 – 8.09 (m, 1H), 8.07 – 7.96 (m, 1H), 7.36 – 7.19 (m, 3H), 7.17 – 7.04 (m, 1H), 5.27 – 5.03 (m, 1H), 4.81 – 4.61 (m, 1H), 3.20 – 3.08 (m, 1H), 2.96 – 2.80 (m, 1H), 2.79 – 2.66 (m, 1H), 2.64 – 2.38 (m, 4H), 2.32 – 1.94 (m, 2H), NH and OH not observed.

The compounds below were prepared according to the procedure of Example 42 by substituting the appropriate starting materials, reagents and reaction conditions.)

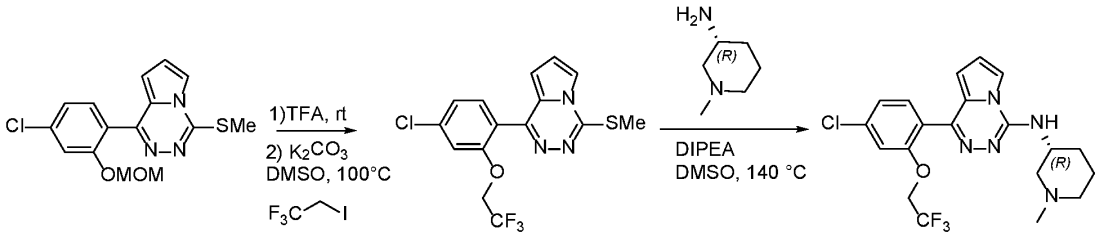
Compound	Spectral Data
I-408	MS *m/z* 312.0 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ: 8.43-8.46 (m, 1H), 7.76 (d, J=8.5 Hz, 1H), 7.51 (d, J=4.1 Hz, 1H), 7.42 (dd, J=4.1, 2.9 Hz, 1H), 7.02-7.09 (m, 2H), 5.26-5.42 (m, 1H), 4.84-4.90 (m, 1H), 3.85 (br dd, J=12.1, 3.7 Hz, 1H), 3.68-3.75 (m, 1H), 3.36-3.50 (m, 1H), 3.15-3.30 (m, 1H), 2.66-2.78 (m, 1H), 2.19-2.40 (m, 1H). OH and NH not observed
I-409	MS *m/z* 426.0 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ: 8.07 (d, J=8.7 Hz, 1H), 7.88 (br s, 1H), 7.25 (d, J=3.7 Hz, 1H), 7.08 (br s, 1H), 6.86-6.93 (m, 2H), 4.96-5.09 (m, 1H), 4.72-4.82 (m, 1H), 3.18-3.31 (m, 1H), 3.05 (br t, J=10.8 Hz, 1H), 2.31-2.48 (m, 5H), 2.22 (br t, J=10.2 Hz, 1H), 1.80-1.99 (m, 1H). OH and NH not observed
I-410	MS *m/z* 410.4 $[M+H]^+$; ^{1}H NMR (400 MHz, Methanol-d4) δ 8.22 – 8.05 (m, 1H), 8.00 – 7.79 (m, 1H), 7.38 – 7.15 (m, 3H), 7.13 – 7.00 (m, 1H), 5.16 – 4.91 (m, 1H), 4.80 – 4.67 (m, 1H), 3.42 – 3.31 (m, 1H), 3.19 – 2.96 (m, 1H), 2.55 – 2.19 (m, 6H), 2.06 – 1.77 (m, 1H). OH and NH not observed.
I-439	MS *m/z* 478.6 $[M+H]^+$; ^{1}H NMR (CD_3OD) δ: 7.68-7.80 (m, 3H), 7.60 (s, 1H), 6.94 (t, *J* = 72 Hz, 1H), 6.83 (bs, 1H), 4.92-5.09 (m, 1H), 4.75-4.83 (m, 1H), 3.23-3.29 (m, 1H), 3.03 (br t, J=10.9 Hz, 1H), 2.30-2.50 (m, 5H), 2.20-2.29 (m, 1H), 1.78-1.99 (m, 1H).NH not observed.
I-444	MS *m/z* 374.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 7.88 (s, 1H), 7.24 (d, J = 7.3 Hz, 1H), 6.89 (s, 1H), 6.65 – 6.56 (m, 2H), 6.32 (s, 1H), 5.01 (d, J = 46.9 Hz, 1H), 4.68 – 4.50 (m, 1H), 3.08 (d, J = 12.26 Hz, 1H), 3.00 – 2.86 (m, 1H), 2.31 (s, 3H), 2.28 – 2.18 (m, 4H), 2.17 – 2.09 (m, 1H), 2.08 – 1.97 (m, 1H), 1.89 – 1.65 (m, 1H), 1H not observed (OH or NH)
I-468	MS *m/z* 462.4 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.90 (d, J = 7.3 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 6.96 (s, 1H), 6.40 (s, 1H), 5.01 (d, J = 46.5 Hz, 1H), 4.70 – 4.55 (m, 1H), 3.14 – 3.03 (m, 1H), 3.00 – 2.88 (m, 1H), 2.35 – 2.11 (m, 5H), 2.09 – 1.98 (m, 1H), 1.89 – 1.65 (m, 1H).
I-478	MS *m/z* 410.6 $[M+H]^+$; ^{1}H NMR (400 MHz, Methanol-d4) δ 8.20 – 8.05 (m, 1H), 7.98 – 7.85 (m, 1H), 7.31 – 7.17 (m, 3H), 7.14 – 7.04 (m, 1H), 4.84 – 4.56 (m, 2H), 3.24 – 3.11 (m, 1H), 2.87 – 2.74 (m, 1H), 2.45 – 2.30 (m, 5H), 2.28 – 2.13 (m, 1H), 2.05 – 1.92 (m, 1H). OH and NH not observed.
I-481	MS *m/z* 394.2, 396.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 6.96 (d, J = 3.5 Hz, 1H), 6.86 (d, J = 9.5 Hz, 2H), 6.65 (d, J = 3.5 Hz, 1H), 5.33 – 5.13 (m, 1H), 3.78 (s, 1H), 3.55 (d, J = 12.6 Hz, 1H), 3.43 (d, J = 12.4 Hz, 1H), 3.16 – 2.95 (m, 1H), 2.80 (s, 3H), 2.57 (s, 1H), 2.31 (t, J = 12.4 Hz, 1H), 2.20 – 1.96 (m, 1H). missing NH and OH peak

Compound	Spectral Data
I-521	MS *m/z* 476.6 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.85 – 7.77 (m, 1H), 7.74 – 7.63 (m, 1H), 7.41 – 7.33 (m, 1H), 7.33 – 7.28 (m, 1H), 7.07 – 6.65 (m, 2H), 6.62 – 6.53 (m, 1H), 5.15 – 4.94 (m, 1H), 4.84 – 4.74 (m, 1H), 3.44 – 3.34 (m, 1H), 3.20 – 3.05 (m, 1H), 2.61 – 2.39 (m, 5H), 2.39 – 2.25 (m, 1H), 2.03 – 1.80 (m, 1H). NH peak not observed
I-535	MS *m/z* : 476.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 8.25 (s, 1H), 8.21 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.02 – 6.88 (m, 1H), 6.40 (d, J = 3.1 Hz, 1H), 5.02 (d, J = 47.9 Hz, 1H), 4.69 – 4.55 (m, 1H), 3.20 – 3.12 (m, 1H), 3.08 – 2.98 (m, 1H), 2.47 – 2.41 (m, 2H), 2.37 – 2.14 (m, 2H), 2.12 – 2.02 (m, 1H), 1.91 – 1.69 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H).
I-538	MS *m/z* : 474.2 $[M+H]^+$; ^{1}HNMR (400 MHz, DMSO–d6) δ : 7.95 (d, J = 1.8 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.70 (s, 1H), 7.40 (t, J = 66.0 Hz, 1H), 7.38 (s, 1H), 7.02 – 6.92 (m, 1H), 6.50 (d, J = 3.8 Hz, 1H), 5.01 (d, J = 47.2 Hz, 1H), 4.68 – 4.55 (m, 1H), 3.18 (d, J = 8.2 Hz, 1H), 3.09 – 2.96 (m, 1H), 2.47 – 2.40 (m, 2H), 2.36 – 2.29 (m, 1H), 2.23 - 2.20 (m, 1H), 2.07 - 2.04 m, 1H), 1.90 – 1.71 (m, 1H), 1.02 (t, J = 7.0 Hz, 3H).
I-571	MS *m/z* 388.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 9.92 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.93 – 6.83 (m, 1H), 6.62 (s, 1H), 6.60 (d, J = 10.4 Hz, 1H), 6.32 (d, J = 3.8 Hz, 1H), 5.01 (d, J = 47.4 Hz, 1H), 4.60 (br s, 1H), 3.18 (d, J = 7.8 Hz, 1H), 3.03 (t, J = 11.8 Hz, 1H), 2.47 – 2.40 (m, 2H), 2.37 – 2.32 (m, 1H), 2.30 (s, 3H), 2.28 – 2.12 (m, 1H), 2.05 (t, J = 10.0 Hz, 1H), 1.91 – 1.69 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H).
I-572	MS *m/z* 414.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO–d6) δ 9.93 (s, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 6.93 – 6.86 (m, 1H), 6.54 (s, 1H), 6.48 (d, J = 11.0 Hz, 1H), 6.34 (d, J = 3.7 Hz, 1H), 5.01 (d, J = 47.6 Hz, 1H), 4.59 (br s, 1H), 3.17 (d, J = 8.9 Hz, 1H), 3.04 (t, J = 12.4 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.36 – 2.13 (m, 2H), 2.06 (t, J = 10.2 Hz, 1H), 1.91 – 1.68 (m, 1H), 1.02 (t, J = 7.1 Hz, 3H).
I-596	MS *m/z* 428.3 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.34 (s, 1H, formic acid proton), 7.82 – 7.54 (m, 2H), 7.41 – 7.09 (m, 2H), 6.95 – 6.72 (m, 1H), 5.24 – 4.99 (m, 1H), 4.84 – 4.69 (m, 1H), 3.57 – 3.41 (m, 1H), 3.31 – 3.19 (m, 1H), 2.80 – 2.33 (m, 6H), 2.10 – 1.81 (m, 1H). NH and OH not observed
I-597	MS *m/z* 408.3 $[M+H-H_2O]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.40 (s, 1H, formic acid proton), 7.72 – 7.59 (m, 1H), 7.56 – 7.48 (m, 1H), 7.28 – 7.19 (m, 1H), 7.19 – 7.14 (m, 1H), 6.60 – 6.54 (m, 1H), 4.49 – 4.38 (m, 1H), 3.97 – 3.87 (m, 1H), 3.40 – 3.32 (m, 1H), 3.19 – 3.09 (m, 1H), 2.59 – 2.46 (m, 2H), 2.35 (s, 3H), 2.26 – 2.02 (m, 2H). NH and OH not observed
I-598	MS *m/z* 458.3 [M+H]+. ^1H NMR (400 MHz, Methanol-d4) δ 8.41 (s, 1H, formic acid proton), 7.79 – 7.49 (m, 2H), 7.04 – 6.69 (m, 3H), 5.23 – 4.97 (m, 1H), 4.84 – 4.67 (m, 1H), 3.64 – 3.43 (m, 1H), 3.40 – 3.32 (m, 1H), 2.93 – 2.58 (m, 3H), 2.55 – 2.36 (m, 2H), 2.09 – 1.84 (m, 1H), 1.31 – 1.14 (m, 3H). NH and OH not observed
I-603	MS *m/z* 472.3 $[M+H-H_2O]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.81 – 7.74 (m, 1H), 7.72 – 7.61 (m, 2H), 7.60 – 7.54 (m, 1H), 6.96 (t, J = 73.1 Hz, 1H),

Compound	Spectral Data
	6.61 – 6.52 (m, 1H), 4.46 – 4.36 (m, 1H), 3.94 – 3.84 (m, 1H), 3.39 – 3.31 (m, 1H), 3.23 – 3.13 (m, 1H), 2.71 – 2.36 (m, 4H), 2.25 – 2.01 (m, 2H), 1.08 – 0.97 (m, 3H). NH and OH not observed
I-605	MS *m/z* 438.3 $[M+H-H_2O]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 7.66 – 7.59 (m, 1H), 7.48 – 7.39 (m, 1H), 6.89 – 6.77 (m, 2H), 6.56 – 6.47 (m, 1H), 4.43 – 4.34 (m, 1H), 3.91 – 3.83 (m, 1H), 3.38 – 3.30 (m, 1H), 3.23 – 3.14 (m, 1H), 2.61 – 2.37 (m, 4H), 2.21 – 1.99 (m, 2H), 1.10 – 0.96 (m, 3H). NH and OH not observed
I-615	MS *m/z* 458.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 7.92 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 15.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.25 – 7.18 (m, 3H), 6.98 – 6.93 (m, 1H), 6.45 (d, J = 2.8 Hz, 1H), 5.01 (d, J = 47.3 Hz, 1H), 4.70 – 4.52 (m, 1H), 3.08 (d, J = 10.7 Hz, 1H), 3.02 – 2.88 (m, 1H),2.36 – 2.11 (m, 5H), 2.06 – 1.98 (m, 1H), 1.87 – 1.65 (m, 1H).
I-617	MS *m/z* : 426.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.77 (dd, J = 2.9, 1.1 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.83 (d, J = 73.5 Hz, 1H), 6.61 – 6.51 (m, 3H), 5.07 – 4.90 (m, 1H), 4.81 – 4.72 (m, 1H), 3.27 – 3.20 (m, 1H), 3.10 – 2.95 (m, 1H), 2.54 – 2.39 (m, 2H), 2.37 (s, 3H), 2.30 – 2.18 (m, 1H), 1.99 – 1.77 (m, 1H). NH and OH not observed
I-619	MS *m/z* : 408.0, 410.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.28 (d, J = 1.7 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.01 (t, J = 72.8 Hz, 1H), 6.75 – 6.72 (m, 1H), 6.96 (s, 1H), 5.35 (d, J = 44.0 Hz, 1H), 4.06 – 3.82 (m, 2H), 3.42 – 3.33 (m, 4H), 3.16 – 3.06 (m, 1H), 2.78 – 2.66 (m, 1H), 2.35 – 2.02 (m, 1H), 1.41 (t, J = 7.3 Hz, 3H). OH and NH not observed.
I-620	MS *m/z* : 408.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.28 (d, J = 1.7 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.01 (dd, J = 9.5, 1.7 Hz, 1H), 6.96 (s, 1H), 5.35 (d, J = 44.0 Hz, 1H), 4.06 – 3.82 (m, 2H), 3.42 – 3.33 (m, 4H), 3.16 – 3.06 (m, 1H), 2.78 – 2.66 (m, 1H), 2.35 – 2.02 (m, 1H), 1.41 (t, J = 7.3 Hz, 3H). NH and OH not observed
I-631	MS *m/z* : 404.1 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.77 (d, J = 2.7 Hz, 1H), 6.95 (t, J = 3.3 Hz, 1H), 6.58 (s, 1H), 6.35 (d, J= 8.1 Hz, 2H), 4.99 (d, J = 46.6 Hz, 2H), 4.78 (s, 1H), 4.08 (q, J = 7.0 Hz, 2H), 3.27 (d, J = 7.9 Hz, 1H), 3.02 (t, J = 10.2 Hz, 1H), 2.44 (d, J = 11.4 Hz, 1H), 2.38 (s, 3H), 2.25 (t, J = 10.2 Hz, 1H), 1.91 (dt, J = 24.8, 11.2 Hz, 1H), 1.43 (t, J = 7.0 Hz, 3H). OH and NH not observed.

Example 43

Preparation of Compound I-485



Step 1: 1-(4-Chloro-2-(2,2,2-trifluoroethoxy)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine

A solution of 1-(4-chloro-2-(methoxymethoxy)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (100 mg, 0.34 mmol, prepared in a manner analogous to Example 38, step 1, using 2-(4-chloro-2-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in place of 2-[2-fluoro-6-(methoxymethoxy)-4-methyl-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane) in TFA (0.3 mL) was stirred at room temperature for 1 hour. Upon completion, TFA was removed under reduced pressure to afford 5-chloro-2-(4-(methylthio)pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol. The crude product was taken to the next step without further purification.

To a solution of 5-chloro-2-(4-(methylthio)pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol (110 mg, 0.38 mmol, 1 eq) in DMSO (2 mL, 0.2 M) is added 2-iodo-1,1,1-trifluoroethane (40 µL, 0.4 mmol, 1.1 eq), and potassium carbonate (110 mg, 0.8 eq, 2.1 eq). The mixture was stirred vigorously at 100℃ for 6 hours. Upon completion the mixture was diluted with ethyl acetate (10 mL) and washed with a 10% aqueous solution of Na_2CO_3 (2 X 10 mL), water (2 X 10 mL), and brine (2 X 10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified on silica gel chromatography eluding with 0-100% ethyl acetate in hexane to afford 1-(4-chloro-2-(2,2,2-trifluoroethoxy)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine as an orange oil (66 mg, 46%). MS *m/z* 374.1, 376.1 $[M+H]^+$.

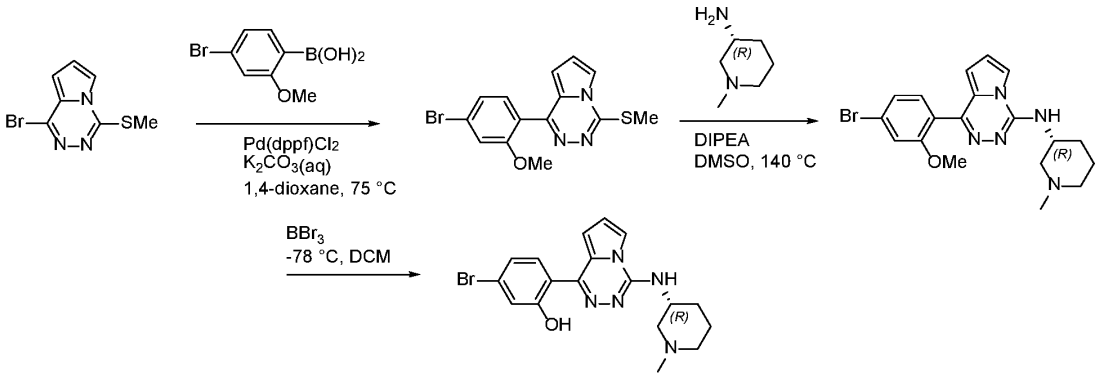
Step 2. (R)-1-(4-Chloro-2-(2,2,2-trifluoroethoxy)phenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine

To a solution of 1-(4-chloro-2-(2,2,2-trifluoroethoxy)phenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (66 mg, 0.18 mmol, 1 eq) in DMSO (300 µL, 0.55 M) was added DIPEA (100 µL, 0.57 mmol, 3.3 eq) and (3R)-1-methylpiperidin-3-amine (62 mg, 0.54 mmol, 3 eq). The resulting mixture was heated to 140℃ for 24 hours. The reaction was then cooled to room

temperature, diluted with 10% *i*-PrOH in DCM (20 mL) and washed with H_2O (3 X 20 mL) and brine (3 X 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified silica gel column chromatography eluting with 0-30% methanol in DCM to afford (R)-1-(4-chloro-2-(2,2,2-trifluoroethoxy)phenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine (20 mg, 28% yield). MS *m/z* 440.3, 442.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.31 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 3.3 Hz, 1H), 6.53 (d, J = 3.7 Hz, 1H), 4.58 (t, J = 8.5 Hz, 2H), 4.54 – 4.38 (m, 1H), 3.33 – 3.18 (m, 2H), 2.83 (d, J = 11.3 Hz, 1H), 2.44 (s, 3H), 2.41 – 2.31 (m, 1H), 2.10 (d, J = 12.4 Hz, 1H), 1.91 (d, J = 14.4 Hz, 1H), 1.86 – 1.55 (m, 2H). NH peak not observed.

Example 44

Preparation of Compound I-484



Step 1: 1-(4-Bromo-2-methoxyphenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine

To a solution of 1-bromo-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (Intermediate 2e, 90 mg, 0.36 mmol, 1 eq) in 1,4-dioxane (1.8 mL, 0.2 M) was added (4-bromo-2-methoxyphenyl)boronic acid (102 mg, 0.43 mmol, 1.2 eq), $Pd(dppf)Cl_2$ (94 mg, 0.1 mmol, 0.25 eq), and K_2CO_3 (2 M in H_2O) (550 µL, 1.1 mL, 3 eq). The resulting mixture was heated to 75˚C for 4 hours. The reaction is then cooled to room temperature, diluted with H_2O (10 mL) and the aqueous phase was extracted with EtOAc (3 X 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography eluting with 0-100% EtOAc in hexanes to afford (4-bromo-2-methoxyphenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine as a yellow oil (51 mg, 42% yield).

Step 2. (R)-1-(4-Bromo-2-methoxyphenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine

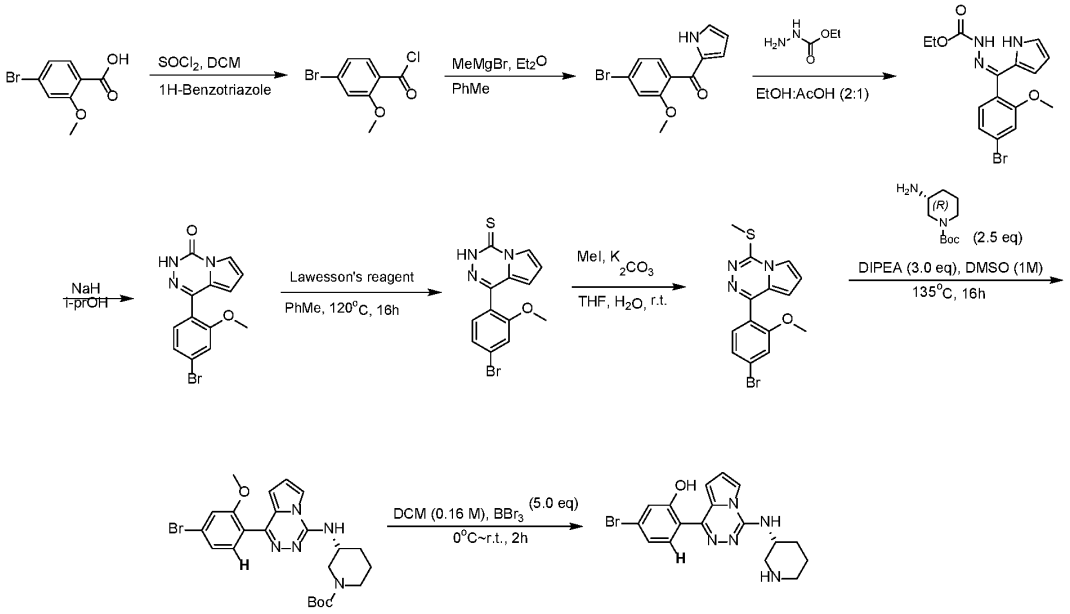
To a solution of (4-bromo-2-methoxyphenyl)-4-(methylthio)pyrrolo[1,2-d][1,2,4]triazine (51 mg, 0.15 mmol, 1 eq) in DMSO (300 uL, 0.5M) was added DIPEA (80 µL, 0.5 mmol, 3.2 eq) and (3R)-1-methylpiperidin-3-amine (34 mg, 0.3 mmol, 2 eq). The resulting mixture was heated to 140℃ for 24 hours. The reaction was then cooled to room temperature, diluted with 10% *i*-PrOH in DCM (20 mL) and washed with H_2O (3X 20 mL) and brine (3X 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified silica gel column chromatography eluting with 0-30% methanol in DCM to afford (R)-1-(4-bromo-2-methoxyphenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine as a yellow oil (46 mg, 0.11 mmol, 72% yield). MS *m/z* 416.3, 418.3 $[M+H]^+$.

Step 3: (R)-5-Bromo-2-(4-((1-methylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol

To a solution of afford (R)-1-(4-bromo-2-methoxyphenyl)-N-(1-methylpiperidin-3-yl)pyrrolo[1,2-d][1,2,4]triazin-4-amine (46 mg, 0.11 mmol, 1 eq) in DCM (400 uL, 0.3M) at -78℃ was added boron tribromide (1.1 mL, 1.1 mmol, 10 eq). The reaction was warmed to room temperature naturally and stirred for 30 minutes. The mixture was then diluted with 10 mL of DCM, cooled to 0℃ and 10% aqueous sodium bicarbonate was added dropwise until a pH of 7 is achieved. The aqueous layer was extracted with 10% i-PrOH in DCM (3 X 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified on silica gel chromatography eluding with 0-30% methanol in DCM to afford (R)-5-bromo-2-(4-((1-methylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol as a pale green solid (8 mg, 35% yield). MS *m/z* 402.2, 404.2 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.96 – 7.81 (m, 2H), 7.27 – 6.96 (m, 4H), 4.47 – 4.38 (m, 1H), 3.28 – 3.13 (m, 1H), 2.90 – 2.76 (m, 1H), 2.55 – 2.34 (m, 5H), 2.17 – 2.02 (m, 1H), 1.87 – 1.52 (m, 3H). NH and OH peak not observed.

Example 45

Preparation of Compound I-490



Step 1. 4-Bromo-2-methoxybenzoyl chloride

To a solution of 4-bromo-2-methoxybenzoic acid (9.00 g, 40.0 mmol, 1.0 eq.) in DCM (80 mL) was added a mixture of 1H-benzotriazole (5.80 g, 48.0 mmol, 1.25 eq.) and $SOCl_2$ (3.5 mL, 48.7 mmol, 1.25 eq.) in DCM (20 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. The mixture was warmed to room temperature and filtered. The filtrate was dried over anhydrous Mg_2SO_4, concentrated in vacuo to give crude 4-bromo-2-methoxybenzoyl chloride (9.7 g) as yellow oil, which was used to the next step without further purification.

Step 2. (4-Bromo-2-methoxyphenyl)(1H-pyrrol-2-yl)methanone

To a solution of CH_3MgBr (3M in THF, 12.9 mL, 38.7 mmol, 1.0 eq.) in Et_2O (30 mL) at 0 °C was added 1H-pyrrole (2.6 g, 38.9 mmol, 1.0 eq.) and the temperature was slowly increased to 40 °C. The reaction mixture was stirred at 40 °C for 1 hour. After cooling to 0 °C, 4-bromo-2-methoxybenzoyl chloride (9.70 g, 38.9 mmol, 1.0 eq,) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to rt and stirred at 40 °C for another1 hour. After Cooling to room temperature, the reaction mixture was quenched with aq. NH_4Cl and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was purified by silica gel

column chromatography eluting with 0-30% EtOAc in hexanes to give 4-bromo-2-methoxyphenyl(1H-pyrrol-2-yl) methanone (5.30 g, 48% yield) as a brown solid. MS *m/z* 280.0, 282.0 $[M+H]^+$.

Step 3. Ethyl (Z)-2-((4-bromo-2-methoxyphenyl)(1H-pyrrol-2-yl)methylene)hydrazine-1-carboxylate

A mixture of (4-bromo-2-methoxyphenyl) (1H-pyrrol-2-yl)methanone (7.63 g, 27.2 mmol, 1.0 eq.), ethyl hydrazinecarboxylate (14.2 g, 136 mmol, 5.0 eq.) in AcOH (27 mL) and EtOH (54 mL) was heated at 100 °C for 16 h. Upon completion, the reaction mixture was cooled to room temperature and concentrated in vacuum. The residue was diluted with water (200 mL), neutralized with aqueous sat. $NaHCO_3$ to pH 8 and extracted with EtOAc (200 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford ethyl (Z)-2-((4-bromo-2-methoxyphenyl) (1H-pyrrol-2-yl) methylene) hydrazine-1-carboxylate (7.1 g, 71% yield) as a purple solid. MS *m/z* 366.2, 368.0 $[M+H]^+$.

Step 4. 1-(4-Bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4(3H)-one

NaH (2.73 g, 68.3 mmol, 2.5 eq.) was added in portions to a stirred solution of ethyl (Z)-2-((4-bromo-2-methoxyphenyl) (1H-pyrrol-2-yl) methylene) hydrazine-1-carboxylate (10.0 g, 27.3 mmol, 1.0 eq.) in isopropyl alcohol (100 mL) at 0 °C. Once the addition was completed, the mixture was heated to 80 °C and stirred at this temperature for 16 hours. Upon completion, the reaction mixture was cooled to room temperature. The mixture was quenched with water (150 mL) and extracted with EtOAc (150 mL x 3). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was treated with EtOAc (35 mL), filtered and washed with EtOAc. The solid was dried under vacuum to afford 1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4(3H)-one (3.70 g, 11.6 mol, 42.5% yield) as a black solid. MS *m/z* 320.0, 322.2 $[M+H]^+$.

Step 5. 1-(4-Bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazine-4(3H)-thione

A mixture of 1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4(3H)-one (1.70 g, 5.31 mmol, 1.0 eq.) and Lawson's reagent (3.22 g, 7.96 mmol, 1.5 eq.) in toluene (53 mL) was heated at 120 °C for 16h. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc (80 mL). The organic phase was washed with aqueous sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 filtered, and concentrated under

reduced pressure. The crude product was triturated with EtOAc (20 mL), filtered and washed with EtOAc. The solid was dried under vacuum to afford 1-(4-bromo-2-methoxyphenyl) pyrrole[1,2-d] [1,2,4] triazin-4(3H)-one (1.10 g, 3.27 mol, 61.6% yield) as a brown solid. MS *m/z* 336.0, 337.9 $[M+H]^+$.

Step 6. 1-(4-Bromo-2-methoxyphenyl)-4-(methylthio) pyrrolo[1,2-d] [1,2,4] triazine

To a mixture of 1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4(3H)-one (1.68 g, 5.00 mmol, 1.0 eq.) and K_2CO_3 (1.73 g, 12.5 mmol, 2.5 eq.) in THF (12 mL) and water (6 mL) was added iodomethane (0.5 mL, 2.28 g/mL, 7.50 mmol, 1.5 eq.) dropwise at 0°C. The reaction was stirred at 0 °C for 1 hour. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexanes to afford 1-(4-bromo-2-methoxyphenyl)-4-(methylthio) pyrrolo[1,2-d] [1,2,4] triazine (1.40 g, 80% yield) as white solids. MS *m/z* 349.9, 352.1 $[M+H]^+$.

Step 7. tert-Butyl (R)-3-((1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4-yl) amino) piperidine-1-carboxylate

A mixture of 1-(4-bromo-2-methoxyphenyl)-4-(methylthio)pyrrolo[1,2-d] [1,2,4] triazine (2.00 g, 5.71 mmol, 1.0 eq.), tert-butyl (R)-3-aminopiperidine-1-carboxylate (2.86 g, 14.3 mmol, 2.5 eq.) and DIPEA (3.00 mL, 0.742 g/mL, 17.1 mmol, 3.0 eq.) in DMSO (4 mL) was heated at 135°C for 16h. Upon completion, the reaction mixture was cooled to room temperature and diluted with water (80 mL) and extracted with EtOAc (80 mL x 3). The organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford tert-butyl (R)-3-((1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4-yl) amino) piperidine-1-carboxylate (1.17 g, 41% yield) as brown solids. MS *m/z* 502.3, 504.4 $[M+H]^+$.

Step 8. (R)-5-Bromo-2-(4-(piperidin-3-ylamino) pyrrolo[1,2-d] [1,2,4] triazin-1-yl) phenol

To a solution of tert-butyl (R)-3-((1-(4-bromo-2-methoxyphenyl) pyrrolo[1,2-d] [1,2,4] triazin-4-yl) amino) piperidine-1-carboxylate (1.17 g, 2.33 mmol, 1.0 eq.) in DCM (10 mL) was added boron tribromide (12 mL, 1.0 M in DCM, 11.7 mmol, 5.0 eq.) dropwise at 0 °C. Once the

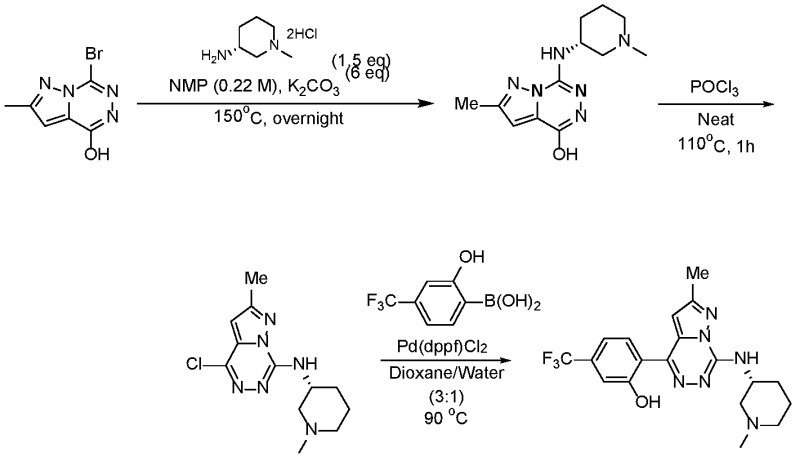
addition was completed, the mixture was warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with MeOH (50 mL) at 0°C slowly and concentrated. The mixture was diluted with water (10 mL), neutralized with aqueous sat. $NaHCO_3$ to pH 8 and extracted with EtOAc (50 mL x 3). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography eluting with 0-10% MeOH in DCM to afford (R)-5-bromo-2-(4-(piperidin-3-ylamino) pyrrole[1,2-d] [1,2,4] triazin-1-yl) phenol (492 mg, 55% yield) as a brown solid. MS *m/z* 388.1, 390.1 $[M+H]^+$; (400 Hz, DMSO-d6) δ: 7.91 (d, J = 8.4 Hz, 1H), 7.46 – 7.45 (m, 1H), 7.22 (d, J = 3.6 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.09 – 7.08 (m, 1H), 4.18 (br s, 1H), 3.27 – 3.23 (m, 2H), 2.91 – 2.88 (m, 1H), 2.56 – 2.53 (m, 1H), 2.09 – 2.07 (m, 1H), 1.75 – 1.71 (m, 1H), 1.65 – 1.50 (m, 2H).

The compounds below were prepared according to the procedure of Example 45 by substituting the appropriate starting materials, reagents, and reaction conditions.

Compound	Spectral Data
I-504	MS *m/z* 470.2, 473.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 2.9 Hz, 1H), 7.72 (dd, *J* = 10.6, 2.6 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.03 – 6.91 (m, 1H), 6.56 (d, *J* = 3.6 Hz, 1H), 4.59 – 4.40 (m, 1H), 3.26 – 3.07 (m, 1H), 2.86 – 2.71 (m, 1H), 2.44 – 2.27 (m, 5H), 2.16 – 2.02 (m, 1H), 1.98 – 1.83 (m, 1H), 1.83 – 1.71 (m, 1H), 1.71 – 1.54 (m, 1H). NH peak not observed.
I-529	MS *m/z* 432.3, 434.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 3.8 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.06 (s, 1H), 4.42 (s, 1H), 3.74 (d, J = 6.2 Hz, 2H), 3.20 (d, J = 10.8 Hz, 1H), 2.79 (d, J = 11.1 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.46 (s, 2H), 2.13 – 1.95 (m, 1H), 1.89 (d, J = 11.4 Hz, 1H), 1.85 – 1.63 (m, 2H). 2H not observed (NH and OH).
I-564	MS *m/z* 416.0, 417.9 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d4) δ 8.43 (s, 1H, formic acid), 7.88 (s, 1H), 7.83 (d, J = 8.00 Hz, 1H), 7.22 – 7.12 (m, 3H), 7.08 (s, 1H), 4.59 – 4.48 (m, 1H), 3.86 – 3.73 (m, 1H), 3.47 – 3.38 (m, 1H), 3.20 – 3.10 (m, 2H), 3.01 – 2.81 (m, 2H), 2.31 – 2.21 (m, 1H), 2.29 – 2.10 (m, 1H), 2.01 – 1.74 (m, 2H), 1.35 (t, J = 6.9 Hz, 3H). 2H not observed (NH and OH).

Example 46

Preparation of Compound I-329



Step 1. (R)-2-Methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-4-ol

A mixture of 7-bromo-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (Intermediate 4a, 3.00 g, 13.2 mmol, 1.0 eq.), (R)-1-methylpiperidin-3-amine hydrochloride (3.69 g, 19.7 mmol, 1.5 eq.) and potassium carbonate (10.9 g, 79.2 mmol, 6.0 eq.) in NMP (60 mL) was heated at 150 °C for 16 h. After cooling to rt, the reaction mixture was filtered and the filtrate was directly purified by reversed-phase column chromatography eluting with 0-100% ACN in H_2O (0.5% NH_4OH) to afford (R)-2-methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-4-ol (1.80 g, 52% yield). MS *m/z* 263.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 6.91 (s, 1H), 6.49 (d, J = 8.2 Hz, 1H), 3.85 – 3.72 (m, 1H), 2.74 – 2.65 (m, 1H), 2.45 – 2.42 (m, 1H), 2.41 (s, 3H), 2.17 (s, 3H), 2.15 – 2.05 (m, 2H), 1.76 – 1.61 (m, 2H), 1.60 – 1.44 (m, 2H).

Step 2. (*R*)-4-Chloro-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine

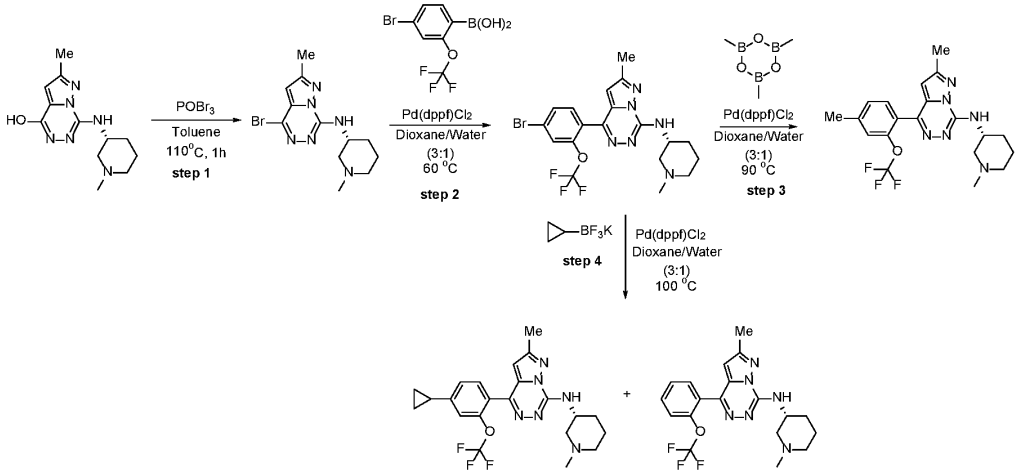
(*R*)-2-Methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-*d*][1,2,4]triazin-4-ol (500.0 mg, 1.906 mmol) was treated with $POCl_3$ (590.4 mg, 3.59 mL, 38.12 mmol). The mixture was then heated at 110 °C for 1 hour, upon which UPLC/MS showed complete conversion to product. The $POCl_3$ was then evaporated under reduced pressure, and the resulting residue was neutralized with saturated $NaHCO_3$ solution until pH > 7. The aqueous layer was then extracted

with CH_2Cl_2 (5×). The organic layer collected was washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The resulting crude (*R*)-4-chloro-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (492.5 mg, 92% yield) was obtained as brown solid and was used without further purification. MS *m/z* 281.3, 283.3 $[M+H]^+$.

Step 3. ((*R*)-2-(2-methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-*d*][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol A mixture of (*R*)-4-chloro-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (50.0 mg, 0.178 mmol), [2-hydroxy-4-(trifluoromethyl)phenyl]boronic acid (44.0 mg, 0.214 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (14.5 mg, 0.0178 mmol), and K_2CO_3 (73.8 mg, 0.534 mmol) was dissolved in dioxane (2.1 mL) and water (0.7 mL). The reaction mixture was then purged and bubbled with nitrogen gas for 5 minutes, followed by stirring and heating at 90 °C for 3 hours. The solvent was evaporated, and the resulting residue was partitioned with water and CH_2Cl_2. The organic layer was collected, dried with Na_2SO_4, and evaporated. The crude product was then purified by flash column chromatography, eluting with 0-10% MeOH in DCM. The compound was purified again with elution of 100% EtOAc for 5 CV followed by gradient elution of CH_2Cl_2:MeOH = 100:0 to 90:10 over 15 CV. (*R*)-2-(2-methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-*d*][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol (24.4 mg, 33.7% yield) was obtained as brown solid. MS *m/z* 407.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.26 (s, 1H), 7.13 (s, 1H), 4.52 – 4.39 (m, 1H), 3.11 – 2.98 (m, 1H), 2.78 – 2.63 (m, 1H), 2.59 (s, 3H), 2.52 – 2.26 (m, 5H), 2.11 – 1.96 (m, 1H), 1.96 – 1.83 (m, 1H), 1.83 – 1.63 (m, 2H). 1 OH and 1 NH signals are not observed.

Example 47

Preparation of Compound I-374, I-396, I-418, and I-419



Step 1. (*R*)-4-Bromo-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine

(*R*)-2-Methyl-7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-*d*][1,2,4]triazin-4-ol (prepared as Example 46, step 1, 300 mg, 1.14 mmol) and $POBr_3$ (1.73 g, 5.72 mmol) were suspended in dry toluene (2.0 mL). The mixture was stirred vigorously and heated to 110 °C for 1 hour. Upon consumption of all starting material, the reaction was carefully quenched with saturated $NaHCO_3$ solution until pH > 7. The aqueous solution was then extracted with CH_2Cl_2 (5×). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The resulting crude (*R*)-4-bromo-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (310.1 mg, 83% yield) was used in the next step without further purification. MS *m/z* 325.3, 327.3 $[M+H]^+$.

Step 2. (*R*)-4-(4-Bromo-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine

A mixture of (*R*)-4-bromo-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (296.9 mg, 0.9128 mmol), (4-bromo-2-(trifluoromethoxy)phenyl)boronic acid (200.0 mg, 0.7022 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (28.7 mg, 0.035 mmol), and K_2CO_3 (291 mg, 2.11 mmol) was dissolved in dioxane (2.1 mL) and water (0.70 mL). The reaction mixture was then purged and bubbled with nitrogen gas for 5 minutes, followed by stirring and heating at 60 °C for 5 hours. The solvent was evaporated, and the

resulting residue was partitioned with water and CH_2Cl_2. The organic layer was collected, dried with Na_2SO_4, and evaporated. The crude product was then purified with C18 reverse phase column (gradient elution of MeCN (0.1% formic acid) : H_2O (0.1% formic acid) = 5 : 95 to 100 : 0 over 20 CV) to obtain (*R*)-4-(4-bromo-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine formic acid salt (96 mg, 22% yield) as white powder. (Small portion (15.0 mg) of the salt was neutralized with $NaHCO_3$ (aq.) to free base for *in vitro* studies). MS *m/z* 485.3, 487.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.83 – 7.69 (m, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 6.51 (s, 1H), 4.60 – 4.47 (m, 1H), 3.10 – 2.92 (m, 1H), 2.91 – 2.27 (m, 8H), 2.22 – 2.05 (m, 1H), 2.05 – 1.92 (m, 1H), 1.92 – 1.67 (m, 2H). 1 CH signal overlaps with solvent peak. 1 NH signal is not observed.

Step 3. (*R*)-2-Methyl-4-(4-methyl-2-(trifluoromethoxy)phenyl)-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine

A mixture of (*R*)-4-(4-bromo-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine formic acid salt (34.0 mg, 0.0701 mmol), trimethylboroxine (26.4 mg, 0.210 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.72 mg, 0.00701 mmol), and K_2CO_3 (290.0 mg, 0.210 mmol) was dissolve in dioxane (2.1 mL) and water (0.7 mL). The reaction mixture was then purged and bubbled with nitrogen gas for 5 minutes, followed by stirring and heating at 90 °C for 16 hours. The solvent was then evaporated under reduced pressure, and the resulting residue was partitioned with water and CH_2Cl_2. The organic layer was collected, dried with Na_2SO_4, and evaporated to dryness. The crude product was then purified by flash column chromatography (gradient elution of CH_2Cl_2:MeOH = 100:0 to 90:10 over 20 CV) to obtain (*R*)-2-methyl-4-(4-methyl-2-(trifluoromethoxy)phenyl)-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (21.9 mg, 74% yield) as pale brown solid. MS *m/z* 421.4 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.34 (s, 1H), 6.45 (s, 1H), 4.51 – 4.43 (m, 1H), 3.05 (s, 1H), 2.83 – 2.13 (m, 11H), 2.12 – 1.57 (m, 5H). 1 NH signal is not observed.

Step 4. (*R*)-4-(4-Cyclopropyl-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine and (*R*)-2-methyl-*N*-(1-methylpiperidin-3-yl)-4-(2-(trifluoromethoxy)phenyl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine

A mixture of (*R*)-4-(4-bromo-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine formic acid salt (30.0 mg, 0.0618

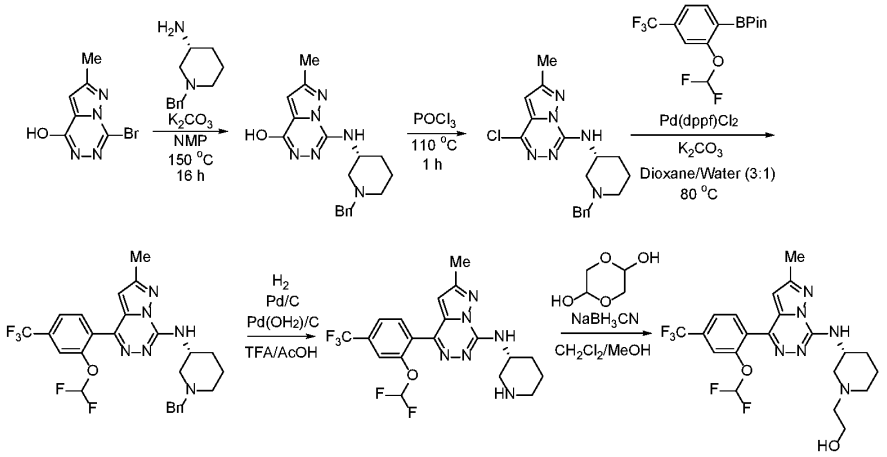
mmol), potassium cyclopropyltrifluoroborate (91.5 mg, 0.618 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (10.1 mg, 0.01236 mmol), and K_2CO_3 (85.4 mg, 0.618 mmol) was dissolved in dioxane (2.1 mL) and water (0.7 mL). The reaction mixture was then purged and bubbled with nitrogen gas for 5 minutes, followed by stirring and heating at 100 °C for 16 hours. The solvent was then evaporated under reduced pressure, and the resulting residue was partitioned with water and CH_2Cl_2. The organic layer was collected, dried with Na_2SO_4, and evaporated to dryness. The crude product was then purified with C18 reverse phase column (gradient elution of MeCN (0.1% formic acid) : H_2O (0.1% formic acid) = 5 : 95 to 100 : 0 over 20 CV) to obtain (*R*)-4-(4-cyclopropyl-2-(trifluoromethoxy)phenyl)-2-methyl-*N*-(1-methylpiperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine formic acid salt (5.6 mg, 20% yield) as white powder and (*R*)-2-methyl-*N*-(1-methylpiperidin-3-yl)-4-(2-(trifluoromethoxy)phenyl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (3.1 mg, 12%) as minor product, respectively.

Compound I-419: MS *m/z* 447 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 8.50 (s, 1H, formate CH), 7.51 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.42 (s, 1H), 4.53 – 4.35 (m, 1H), 3.23 – 3.03 (m, 1H), 2.89 – 2.70 (m, 1H), 2.70 – 2.14 (m, 8H), 2.14 – 1.96 (m, 2H), 1.96 – 1.82 (m, 1H), 1.83 – 1.59 (m, 2H), 1.22 – 0.93 (m, 2H), 0.93 – 0.62 (m, 2H). 1 NH signals not observed.

Compound I-420:: MS *m/z* 407 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 8.52 (s, 1H, formate CH), 7.83 – 7.62 (m, 2H), 7.62 – 7.41 (m, 2H), 6.48 (s, 1H), 4.61 – 4.47 (m, 1H), 3.16 – 2.80 (m, 2H), 2.80 – 2.27 (m, 7H), 2.17 – 2.04 (m, 1H), 2.04 – 1.90 (m, 1H), 1.90 – 1.67 (m, 2H). 1 NH signal not observed. 1 CH signal overlaps with solvent peak.

Example 48

Preparation of Compound I-375



Step 1. (*R*)-7-((1-Benzylpiperidin-3-yl)amino)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-4-ol

A mixture of 7-bromo-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-4-ol (200 mg, 0.87 mmol) and (*R*)-1-benzylpiperidin-3-amine (831 mg, 4.37 mmol) in dry NMP (4.5 mL) was stirred under nitrogen atmosphere at 150 °C for 16 hours. After all starting material has been consumed, the solution was diluted with EtOAc. It was then washed with saturated $NaHCO_3$ solution (3×), water (3×), and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was then purified by flash column chromatography (gradient elution of CH_2Cl_2 : MeOH = 100:0 to 90:10 over 20 CV). (*R*)-7-((1-benzylpiperidin-3-yl)amino)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-4-ol (298 mg, > 99% yield) was obtained as yellow foam. MS *m/z* 339.4 $[M+H]^+$.

Step 2. (*R*)-*N*-(1-Benzylpiperidin-3-yl)-4-chloro-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine

(*R*)-7-((1-Benzylpiperidin-3-yl)amino)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-4-ol (200.0 mg, 0.5910 mmol) was treated with $POCl_3$ (1.81 g, 1.10 mL, 11.8 mmol). The reaction was stirred and heated at 110 °C for 1 hour. After consumption of the starting material, the $POCl_3$ was evaporated under reduced pressure, and the resulting residue was neutralized with saturated $NaHCO_3$ solution until pH > 7. The aqueous layer was then extracted with CH_2Cl_2 (5×). The organic layer collected was washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The resulting crude (*R*)-*N*-(1-benzylpiperidin-3-yl)-4-chloro-2-methylpyrazolo[1,5-

d][1,2,4]triazin-7-amine (203 mg, 96% yield) was obtained as brown solid and used in the next step without further purification. MS *m/z* 357.4, 359.4 $[M+H]^+$.

Step 3. (*R*)-*N*-(1-Benzylpiperidin-3-yl)-4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine

A mixture of (*R*)-*N*-(1-benzylpiperidin-3-yl)-4-chloro-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine (150 mg, 0.42 mmol), 2-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (171 mg, 0.50 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (34 mg, 0.042 mmol), and K_2CO_3 (174 mg, 1.26 mmol) was dissolved in dioxane (3.0 mL) and water (1.0 mL). The reaction mixture was then purged and bubbled with nitrogen gas for 5 minutes, followed by stirring and heating at 80 °C for 1 hours. The solvent was evaporated, and the resulting residue was partitioned with water and CH_2Cl_2. The organic layer was collected, dried with Na_2SO_4, and evaporated. The crude product was then purified by flash column chromatography (gradient elution of CH_2Cl_2:MeOH = 100:0 to 90:10 over 20 CV). (*R*)-*N*-(1-benzylpiperidin-3-yl)-4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine was obtained along with inseparable impurities (total 248 mg), which was used in the next step without further purification. MS *m/z* 533.4 $[M+H]^+$.

Step 4. (*R*)-*N*-(1-Benzylpiperidin-3-yl)-4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine

Crude (*R*)-*N*-(1-benzylpiperidin-3-yl)-4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-amine (50.0 mg, 0.282 mmol) in THF (2.0 mL) and acetic acid (1.0 mL) was treated with wet Pd/C (10% wt, 5.0 mg) and $Pd(OH_2)$/C (20% wt, 5.0 mg). The flask was then purged with hydrogen and the reaction was stirred for 16 hours. After all starting material has been consumed, the mixture was filtered over a pad of celite. The filtrate was then treated saturated $NaHCO_3$ solution until pH > 7. The aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic layer was then washed with water and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by flash column chromatography (gradient elution of CH_2Cl_2:MeOH = 90:10 to 65:35) to obtain (*R*)-4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methyl-*N*-(piperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (33.4 mg, 80% yield) as brown solid. MS *m/z* 443.4 $[M+H]^+$.

Step 5. (*R*)-2-(3-((4-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-yl)amino)piperidin-1-yl)ethan-1-ol

(*R*)-4-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methyl-*N*-(piperidin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-7-amine (33.4 mg, 0.0755 mmol) and 1,4-dioxane-2,5-diol (6.80 mg, 0.0566 mmol) were dissolved in CH_2Cl_2 (1.0 mL) and MeOH (1.0 mL). Into the solution was then added sodium cyanoborohydride (5.69 mg, 0.0906 mmol). The solution was stirred for 10 minutes, upon which complete formation to product was observed by UPLC/MS. The reaction was then quenched with addition of saturated $NaHCO_3$ solution dropwise. The solution was partitioned with CH_2Cl_2 and water. The organic layer was collected, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified with flash column chromatography (gradient elution of CH_2Cl_2:MeOH = 100:0 to 80:20) to obtain (*R*)-2-(3-((4-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-*d*][1,2,4]triazin-7-yl)amino)piperidin-1-yl)ethan-1-ol (22.4 mg, 61%) as white solid. MS *m/z* 487.4 $[M+H]^+$; (400 MHz, CD3OD) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.67 (s, 1H), 6.94 (t, *J* = 73.0 Hz, 1H), 6.49 (s, 1H), 4.54 – 4.43 (m, 1H), 3.79 – 3.66 (m, 2H), 3.11 – 2.98 (m, 1H), 2.87 – 2.29 (m, 8H), 2.07 – 1.93 (m, 1H), 1.92 – 1.63 (m, 3H). 1 OH and 1 NH signals are not observed.

The compounds below were prepared according to the procedure of Example 48 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-327	MS *m/z* 377.4 [M-H]-; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.76 (d, J = 8.1 Hz, 1H), 7.03 (s, 1H), 6.73 - 6.64 (m, 2H), 4.37 (td, J = 4.1, 7.9 Hz, 1H), 3.06-2.92 (m, 1H), 2.68-2.53 (m, 4H), 2.44-2.26 (m, 5H), 2.07 - 1.95 (m, 1H), 1.95 - 1.81 (m, 2H), 1.81 - 1.60 (m, 2H), 1.08 - 0.96 (m, 2H), 0.79 - 0.69 (m, 2H); 2H (OH and NH) wasn't observed
I-328	MS *m/z* 395.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (d, J = 8.8 Hz, 1H), 7.12 (s, 1H), 6.60 (dd, J = 8.9, 2.5 Hz, 1H), 6.54 (d, J = 2.5 Hz, 1H), 4.44 – 4.31 (m, 1H), 3.84 (s, 3H), 3.09 – 2.91 (m, 1H), 2.68 – 2.59 (m, 1H), 2.57 (s, 3H), 2.48 – 2.22 (m, 5H), 2.09 – 1.93 (m, 1H), 1.93 – 1.80 (m, 1H), 1.80 – 1.60 (m, 2H). 1 OH and 1 NH signals are not observed.
I-330	MS *m/z* 457.4 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 6.93 (t, J = 73.0 Hz, 1H), 6.49 (s, 1H), 4.53 – 4.42 (m, 1H), 3.09 – 2.95 (m, 1H), 2.74 – 2.57 (m, 1H), 2.53 (s, 3H), 2.46 – 2.22 (m, 5H), 2.12 – 1.95 (m, 1H), 1.95 – 1.81 (m, 1H), 1.81 – 1.60 (m, 2H). 1 CH signal overlaps with solvent peak. 1 NH signal not observed.
I-334	MS *m/z* 416.5, 418.5 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.17 - 7.08 (m, 2H), 7.08 - 7.03 (m, 1H), 4.45-4.36 (m, 1H), 3.10-2.94 (m, 1H), 2.71 - 2.61 (m, 1H), 2.61 - 2.54 (m, 3H), 2.46-2.28 (m, 5H),

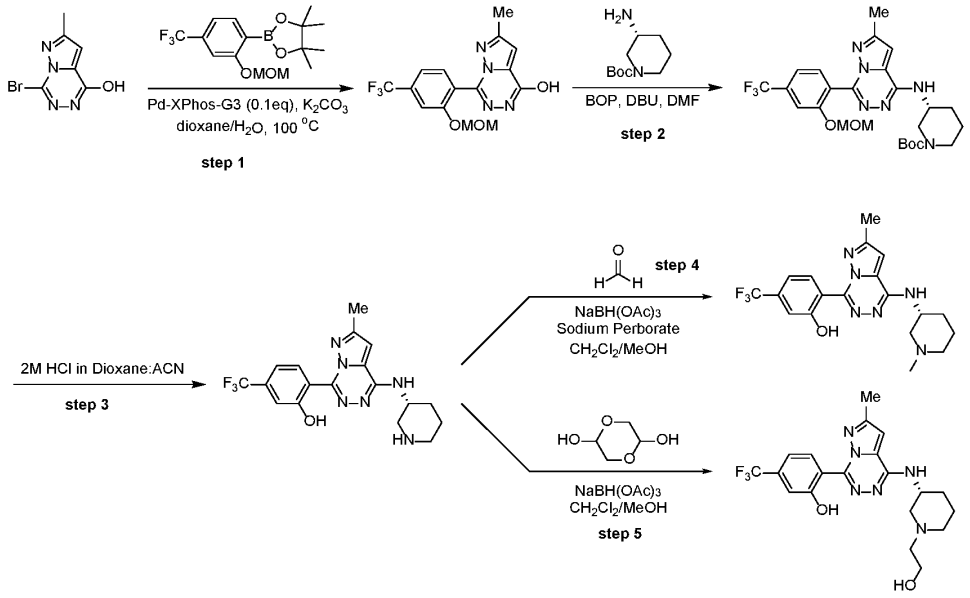
Compound	Spectral Data
	2.09 - 1.96 (m, 1H), 1.93 - 1.81 (m, 1H), 1.81 - 1.63 (m, 2H); 2H (OH and NH) wasn't observed
I-345	MS *m/z* 433.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 7.04 (s, 1H), 4.53 – 4.40 (m, 1H), 3.12 – 3.02 (m, 1H), 2.79 – 2.67 (m, 1H), 2.59 – 2.31 (m, 5H), 2.31 – 2.22 (m, 1H), 2.08 – 1.96 (m, 1H), 1.96 – 1.83 (m, 1H), 1.83 – 1.67 (m, 2H), 1.22 – 1.11 (m, 2H), 1.11 – 1.01 (m, 2H). 1 OH and 1 NH signals are not observed.
I-346	MS *m/z* 483.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66 (s, 1H), 6.95 (t, *J* = 72.9 Hz, 1H), 6.38 (s, 1H), 4.56 – 4.39 (m, 1H), 3.08 – 2.94 (m, 1H), 2.71 – 2.56 (m, 1H), 2.53 – 2.24 (m, 5H), 2.24 – 2.14 (m, 1H), 2.09 – 1.95 (m, 1H), 1.94 – 1.81 (m, 1H), 1.81 – 1.61 (m, 2H), 1.15 – 1.03 (m, 2H), 1.01 – 0.87 (m, 2H).1 NH signal is not observed.
I-347	MS *m/z* 395.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 8.8 Hz, 1H), 7.01 (s, 1H), 6.60 (dd, J = 8.8, 2.5 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 4.45 – 4.30 (m, 1H), 3.83 (s, 3H), 3.09 – 2.89 (m, 1H), 2.73 – 2.56 (m, 1H), 2.52 – 2.29 (m, 5H), 2.29 – 2.18 (m, 1H), 2.07 – 1.93 (m, 1H), 1.93 – 1.80 (m, 1H), 1.80 – 1.63 (m, 2H), 1.19 – 1.09 (m, 2H), 1.09 – 1.00 (m, 2H). 1 OH and 1 NH signals are not observed.
I-359	MS *m/z* 371.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 6.63 (s, 1H), 6.59 (d, J = 10.7 Hz, 1H), 6.41 (s, 1H), 4.53 – 4.37 (m, 1H), 3.11 – 2.94 (m, 1H), 2.72 – 2.57 (m, 1H), 2.51 (s, 3H), 2.45 – 2.16 (m, 8H), 2.08 – 1.95 (m, 1H), 1.95 – 1.80 (m, 1H), 1.80 – 1.63 (m, 2H). 1 OH and 1 NH signals are not observed.
I-363	MS *m/z* 425.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 7.16 – 6.96 (m, 2H), 6.44 (s, 1H), 4.59 – 4.37 (m, 1H), 3.17 – 2.97 (m, 1H), 2.79 – 2.62 (m, 1H), 2.59 – 2.31 (m, 8H), 2.15 – 1.96 (m, 1H), 1.96 – 1.82 (m, 1H), 1.82 – 1.62 (m, 2H). 1 OH and 1 NH signals are not observed.
I-381	MS *m/z* 421.4 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 7.52 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 8.5, 2.6 Hz, 1H), 6.30 (s, 1H), 4.54 – 4.38 (m, 1H), 3.94 (s, 3H), 3.19 – 2.90 (m, 2H), 2.82 – 2.15 (m, 7H), 2.15 – 1.55 (m, 5H). 1 NH signal is not observed.
I-382	MS *m/z* 459.4 $[M+H]^+$; ^1H NMR (500 MHz, CD_3OD) δ 8.20 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 6.37 (s, 1H), 4.55 – 4.42 (m, 1H), 3.14 – 2.98 (m, 1H), 2.76 – 2.61 (m, 1H), 2.51 (s, 3H), 2.44 – 2.24 (m, 4H), 2.13 – 1.62 (m, 5H). 1 NH signal is not observed.
I-429	MS *m/z* 397.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 6.53 (s, 1H), 6.47 (d, J = 11.1 Hz, 1H), 6.43 (s, 1H), 4.54 – 4.38 (m, 1H), 3.13 – 2.97 (m, 1H), 2.78 – 2.61 (m, 1H), 2.51 (s, 3H), 2.46 – 2.29 (m, 5H), 2.11 – 1.98 (m, 1H), 1.96 – 1.86 (m, 2H), 1.79 – 1.66 (m, 2H), 1.08 – 0.99 (m, 2H), 0.80 – 0.69 (m, 2H). 1 OH and 1 NH signals are not observed.
I-455	MS *m/z* 391.5, 393.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H, formate CH), 6.96 – 6.74 (m, 2H), 6.44 (s, 1H), 4.61 – 4.44 (m, 1H), 3.27 (m, 1H, overlapped with CD_3OD peak),3.08 – 2.76 (m, 2H), 2.76 – 2.30 (m, 7H), 2.20 – 2.05 (m, 1H), 2.05 – 1.91 (m, 1H), 1.91 – 1.68 (m, 2H). OH and NH not observed.

Compound	Spectral Data
I-515	MS *m/z* 385.6 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 6.63 (s, 1H), 6.59 (d, *J* = 11.6 Hz, 1H), 6.42 (s, 1H), 4.53 – 4.40 (m, 1H), 3.20 – 3.08 (m, 1H), 2.83 – 2.69 (m, 1H), 2.56 (q, *J* = 7.6 Hz, 2H), 2.51 (s, 3H), 2.48 – 2.28 (m, 5H), 2.10 – 1.98 (m, 1H), 1.94 – 1.83 (m, 1H), 1.83 – 1.65 (m, 2H), 1.16 (t, *J* = 7.3 Hz, 3H). 1 OH and 1 NH signals are not observed.
I-550	MS *m/z* 397.4 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.04 (s, 1H), 6.79 (s, 2H), 4.44 – 4.32 (m, 1H), 3.20 – 3.00 (m, 1H), 2.79 – 2.67 (m, 1H), 2.61 – 2.52 (m, 3H), 2.53 – 2.37 (m, 5H), 2.33 (s, 3H), 2.09 – 1.95 (m, 1H), 1.95 – 1.82 (m, 1H), 1.82 – 1.62 (m, 2H). NH and OH peak not observed.
I-551	MS *m/z* 387.4 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 6.63 (s, 1H), 6.59 (d, J = 11.6 Hz, 1H), 6.42 (s, 1H), 4.53 – 4.40 (m, 1H), 3.20 – 3.08 (m, 1H), 2.83 – 2.69 (m, 1H), 2.56 (q, J = 7.6 Hz, 2H), 2.51 (s, 3H), 2.48 – 2.28 (m, 5H), 2.10 – 1.98 (m, 1H), 1.94 – 1.83 (m, 1H), 1.83 – 1.65 (m, 2H), 1.16 (t, J = 7.3 Hz, 3H). NH and OH peak not observed.
I-554	MS *m/z* 411.6 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 6.53-6.59 (m, 1H), 6.43-6.53 (m, 2H), 4.53 (br s, 1H), 3.36-3.50 (m, 1H), 2.94-3.17 (m, 1H), 2.83 (br s, 2H), 2.58-2.76 (m, 2H), 2.53 (br s, 3H), 2.14 (br s, 1H), 1.88-2.05 (m, 2H), 1.70-1.88 (m, 2H), 1.25 (br t, J=6.6 Hz, 3H), 1.05 (br d, J=6.8 Hz, 2H), 0.76 (br s, 2H). OH and NH not observed.
I-555	MS *m/z* 401.6 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 6.45 (s, 1H), 6.42 – 6.28 (m, 2H), 4.56 – 4.40 (m, 1H), 3.82 (s, 3H), 3.22 – 3.10 (m, 1H), 2.90 – 2.72 (m, 1H), 2.70 – 2.56 (m, 2H), 2.56 – 2.35 (m, 5H), 2.11 – 2.02 (m, 1H), 1.95 – 1.85 (m, 1H), 1.80 – 1.69 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H). 1 OH and 1 NH signals are not observed.
I-556	MS *m/z* 471.6 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7.84 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.67 (s, 1H), 6.93 (t, J = 73.0 Hz, 1H), 6.49 (s, 1H), 4.54 – 4.43 (m, 1H), 3.17 – 3.00 (m, 1H), 2.78 – 2.65 (m, 1H), 2.61 – 2.47 (m, 5H), 2.47 – 2.26 (m, 2H), 2.11 – 1.97 (m, 1H), 1.94 – 1.81 (m, 1H), 1.81 – 1.64 (m, 2H), 1.15 (t, J = 7.3 Hz, 3H). 1 NH signal is not observed.
I-560	MS *m/z* 421.4 $[M+H]^+$; ^1H NMR (500 MHz, MeOD) δ 7.14 (s, 1H), 7.04 (d, J = 1.6 Hz, 1H), 6.30 (s, 1H), 4.47 (dd, J = 8.8, 3.8 Hz, 1H), 3.18-3.10 (m, 1H), 2.88 – 2.68 (m, 1H), 2.50 (s, 3H), 2.32-2.42 (m, 5H), 2.15 (s, 3H), 2.04 (d, J = 13.8 Hz, 1H), 1.89 (dt, J = 14.5, 4.6 Hz, 1H), 1.83 – 1.63 (m, 2H). NH and OH peak not observed.
I-579	MS *m/z* 405, 407 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 6.89 – 6.77 (m, 2H), 6.42 (s, 1H), 4.54 – 4.42 (m, 1H), 3.21 – 3.10 (m, 1H), 2.85 – 2.70 (m, 1H), 2.57 (q, J = 7.4 Hz, 2H), 2.52 (s, 3H), 2.48 – 2.33 (m, 2H), 2.11 – 2.00 (m, 1H), 1.95 – 1.82 (m, 1H), 1.82 – 1.66 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H). 1 OH and 1 NH signals are not observed.
I-584	MS *m/z* 437 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 7 7.87 (br dd, J=5.9, 1.4 Hz, 1H), 7.28 (br s, 1H), 6.92-7.10 (m, 2H), 4.54-4.75 (m, 1H), 3.86-3.97 (m, 1H), 3.62-3.71 (m, 1H), 2.95-3.07 (m, 2H), 2.64 (br s, 3H), 2.27-2.44 (m, 1H), 2.13-2.26 (m, 1H), 1.87-2.09 (m, 2H), 1.38-1.46 (m, 2H), 1.15-1.33 (m, 3H)1 OH and 1 NH signals are not observed.

Compound	Spectral Data
I-585	MS *m/z* 473.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.19 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 6.36 (s, 1H), 4.55 – 4.43 (m, 1H), 3.12 – 3.03 (m, 1H), 2.77 – 2.66 (m, 1H), 2.62 – 2.48 (m, 5H), 2.48 – 2.30 (m, 2H), 2.10 – 1.99 (m, 1H), 1.93 – 1.81 (m, 1H), 1.81 – 1.65 (m, 2H), 1.15 (t, J = 7.3 Hz, 3H). 1 NH signal is not observed.

Example 49

Preparation of Compounds I-332, I-336, and I-338



Step 1. 7-(2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol

A mixture of 7-bromo-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (Intermediate 4a, 3.50 g, 15.3 mmol, 1.0 eq.), 2-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.2 g, 30.6 mmol, 2.0 eq.), $XPhosPdG_3$ (1.30 g, 1.53 mmol, 0.1 eq.) and potassium carbonate (6.34 g, 45.9 mmol, 3.0 eq.) in water (7 mL) and 1,4-dioxane (35 mL) was heated at 100°C for 16 h under nitrogen. Upon completion, the reaction mixture was cooled to room temperature and diluted with water (150 mL). The mixture was extracted with EtOAc (150 mL x 3). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-50% EtOAc in hexanes to afford 7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-

methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (1.60 g, 4.52 mmol, 29.5% yield) as an off-white solid. MS *m/z* 355.1 $[M+H]^+$. ^1H NMR (400Hz, DMSO-d6) δ: 12.62 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.57 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.07 (s, 1H), 5.26 (s, 2H), 3.26 (s, 3H), 2.31 (s, 3H).

Step 2. tert-Butyl (R)-3-((7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methyl pyrazolo[1,5-d][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate

To a mixture of 7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-ol (248 mg, 0.70 mmol, 1 eq), *tert*-butyl (3R)-3-aminopiperidine-1-carboxylate (421 mg, 2.10 mmol, 3 eq) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.28 mL, 1.75 mmol, 2.5 eq) in DMF (4.7 mL) was added BOP (358 mg, 0.77 mmol, 1.1 eq) at 0 ºC. The reaction mixture was allowed to slowly return to room temperature and stirred overnight. Upon completion, the reaction mixture was diluted with a small amount of $NaHCO_3$ (sat. aq.), extracted several times with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified first by silica gel column chromatography eluting with 0:100 to 10:90 MeOH:DCM to afford tert-butyl (R)-3-((7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate as an impure oil which was used without further purification.$^+$

Step 3. (R)-2-(2-Methyl-4-(piperidin-3-ylamino)pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol

The product from step 2 was suspended in ACN (4 mL) and 4 M HCl in Dioxane (2 mL) and stirred at room temperature for 2 h. Upon reaction completion solvents were removed in vacuo. The residue was concentrated several times from dichloromethane to remove excess HCl. The crude residue was purified first by silica gel column chromatography eluting with 0:100 to 20:80 (10% NH4OH in MeOH):DCM to afford (R)-2-(2-methyl-4-(piperidin-3-ylamino)pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol (176 mg, 53% over two steps). MS *m/z* 393.4 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.95 (d, J = 8.3 Hz, 1H), 7.27 – 7.19 (m, 2H), 6.97 (s, 1H), 4.28 – 4.14 (m, 1H), 3.45 – 3.31 (m, 1H), 3.07 – 2.94 (m, 1H), 2.75 – 2.56 (m, 2H), 2.53 (s, 3H), 2.25 – 2.12 (m, 1H), 1.91 – 1.77 (m, 1H), 1.78 – 1.60 (m, 2H), three exchangeable protons not observed.

Step 4. (R)-2-(2-Methyl-4-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol

A mixture of (R)-7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methyl-N-

(piperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-4-amine (70 mg, 0.18 mmol, 1 eq) and sodium perborate tetrahydrate (82 mg, 0.54 mmol, 3 eq) in DCM (2 mL) and methanol (400 µL) was stirred for 30 min at 0 °C. After 30 min, formaldehyde (37 wt% in water) (40 µL, 0.54 mmol, 3 eq) followed by sodium triacetoxyborohydride (113 mg, 0.54 mmol, 3 eq). The reaction was stirred at 0 °C for 1 min. The ice bath was removed, and the reaction mixture was stirred for 2 min. The reaction was quenched by addition a small amount of $NaHCO_3$ (sat, aq.) and a small amount of water followed by extraction with DCM. The combined organic extracts were dried over sodium sulfate and the crude material was purified by flash column chromatography 0:100 to 10:90 (10% NH4OH in MeOH):DCM to afford (R)-2-(2-methyl-4-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol (45 mg, 62%). MS *m/z* 407.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 (d, J = 8.5 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.96 (s, 1H), 4.45 – 4.31 (m, 1H), 3.17 – 3.05 (m, 1H), 2.82 – 2.65 (m, 1H), 2.54 (s, 3H), 2.35 (s, 3H), 2.28 – 2.15 (m, 2H), 2.13 – 2.00 (m, 1H), 1.91 – 1.67 (m, 2H), 1.62 – 1.47 (m, 1H), NH and OH not observed.

Step 5. (R)-2-(4-((1-(2-Hydroxyethyl)piperidin-3-yl)amino)-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol

1,4-Dioxane-2,5-diol (20 mg, 0.16 mmol, 1 eq) followed by sodium triacetoxyborohydride (102 mg, 0.48 mmol, 3 eq) were added to a solution of (R)-7-(2-(methoxymethoxy)-4-(trifluoromethyl)phenyl)-2-methyl-N-(piperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-4-amine (63 mg, 0.16 mmol, 1 eq) in DCM (2 mL) and methanol (400 µL) at 0 °C. The ice bath was removed, and the mixture was stirred at room temperature for 30 min. The reaction was quenched by addition a small amount of NaHCO3 (sat. aq.) and a small amount of water followed by extraction with DCM. The combined organic extracts were dried over sodium sulfate and the crude material was purified by flash column chromatography 0:100 to 20:80 (10% NH4OH in MeOH):DCM to afford (R)-2-(4-((1-(2-hydroxyethyl)piperidin-3-yl)amino)-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol (48 mg, 69%). MS *m/z* 437.5 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.02 (d, J = 8.5 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.00 (s, 1H), 4.44 – 4.31 (m, 1H), 3.79 – 3.64 (m, 2H), 3.21 – 3.06 (m, 1H), 2.80 – 2.67 (m, 1H), 2.67 – 2.48 (m, 5H), 2.45 – 2.26 (m, 2H), 2.09 – 1.93 (m, 1H), 1.90 – 1.79 (m, 1H), 1.79 – 1.55 (m, 2H), NH and 2 OH not observed.

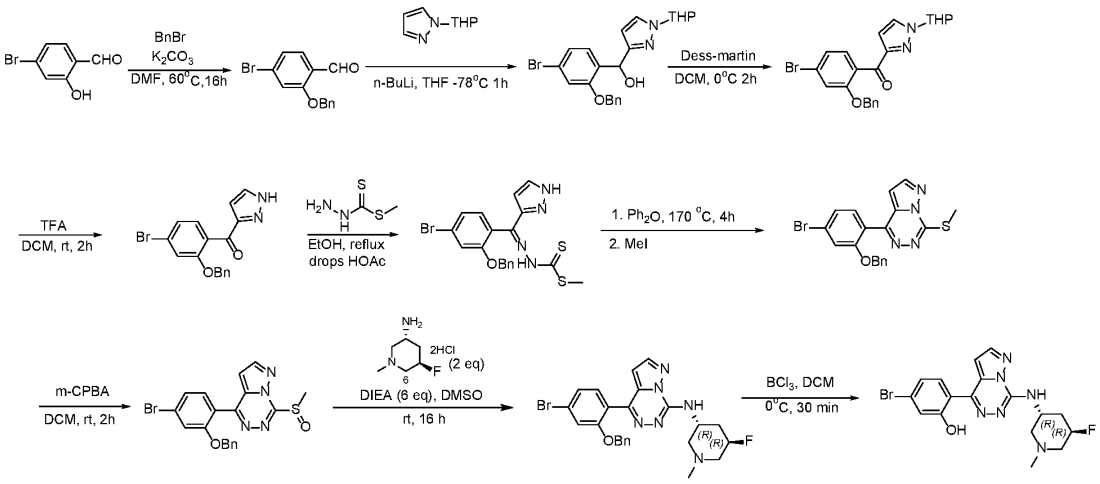
The compounds below were prepared according to the procedure of Example 49 by

substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-339	MS *m/z* 355.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 8.97 (d, J = 9.0 Hz, 1H), 6.94 (s, 1H), 6.57 (s, 2H), 4.43 – 4.30 (m, 1H), 3.85 (s, 3H), 3.72 – 3.62 (m, 1H), 3.37–3.32 (m, 1H), 3.01 – 2.86 (m, 2H), 2.55 (s, 3H), 2.28 – 2.18 (m, 1H), 2.13 – 2.03 (m, 1H), 1.97 – 1.73 (m, 2H). NH and OH not observed
I-351	MS *m/z* 369.4 $[M+H]^+$; ^1H NMR (400 MHz, Methanol-d4) δ 9.04 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 6.61 – 6.51 (m, 2H), 4.39 – 4.27 (m, 1H), 3.84 (s, 3H), 3.19 – 3.03 (m, 1H), 2.81 – 2.67 (m, 1H), 2.55 (s, 3H), 2.35 (s, 3H), 2.32 – 2.14 (m, 2H), 2.13 – 1.97 (m, 1H), 1.93 – 1.67 (m, 2H), 1.65 – 1.44 (m, 1H).

Example 50

Preparation of Compound I-546



Step 1. 2-(Benzyloxy)-4-bromobenzaldehyde

To a solution of compound 4-bromo-2-hydroxy-benzaldehyde (10.0 g, 49.7 mmol) in DMF (100 mL) was added (bromomethyl)benzene (10.2 g, 59.6 mmol) and K_2CO_3(17.2 g, 124 mmol). The reaction mixture was stirred at 60°C under N_2 for 16 hours, then cooled to room temperature. The mixture was filtered and the filtrate was concentrated under reduce pressure. The residue was diluted with DCM (150 mL) and washed with brine (2 x 50 mL), dried over anhydrous Na2SO4, evaporated in vacuum, and the crude product was purified on silica gel eluted with (PE/EA=1:10) to give the compound 2-benzyloxy-4-bromo-benzaldehyde (14.0 g, 96.7% Yield) as a white solid.

Step 2. (2-(Benzyloxy)-4-bromophenyl)(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanol

To a solution of 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (12.34 g, 80.27 mmol) in THF (300 mL) was added n-BuLi in hexanes (46.5 mL, 120 mmol, 2.5 mol/L) at -65°C over 30 min. The mixture was stirred at 0-10°C for 10-20 min. Then a solution of 2-benzyloxy-4-bromo-benzaldehyde (19.6 g, 67.3 mmol) in THF (100 mL) was added dropwise at -65°C for 30 min. The reaction mixture was stirred at -65°C under N_2 for 2 hours, the mixture was quenched by sat. NH_4Cl (150 mL) and extracted with EtOAc(100 mL x 3). The organic layer was combined and washed with brine (50 mL × 2), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel eluted with (PE/EA=1:10) to give the compound (2-(benzyloxy)-4-bromophenyl)(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanol (13.0 g, 43.8% Yield) as a pale yellow oil. MS *m/z* 443, 445 $[M+H]^+$.

Step 3. (2-(Benzyloxy)-4-bromophenyl)(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanone

To a solution of (2-benzyloxy-4-bromo-phenyl)-(1-tetrahydropyran-2-ylpyrazol-3-yl)methanol (13.0 g, 29.41 mmol) in DCM (130 mL) was added Dess-Martin (18.7 g, 44.11 mmol) under N_2 at 0°C for 2 h. The sat. $NaHCO_3$ (200mL) was added and extracted with DCM (250mL x 2). the organic layer was combined and washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on silica gel eluted with (PE/EA=1:4) to give the compound (2-(benzyloxy)-4-bromophenyl)(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanone (9.3 g, 43.8% Yield) as a pale yellow oil. MS *m/z* 441, 443 $[M+H]^+$.

Step 4. (2-(Benzyloxy)-4-bromophenyl)(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanone

To a solution of compound (2-benzyloxy-4-bromo-phenyl)-(1-tetrahydropyran-2-ylpyrazol-3-yl)methanone (9.3 g, 21.1 mmol) in DCM (80 mL) was added TFA (20 mL, 264.5 mmol). The reaction mixture was stirred at RT for 2 h. The solvents was removed under reduce pressure. The residue was diluted with DCM (150 mL) and washed with saturated $NaHCO_3$(2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the compound (2-(benzyloxy)-4-bromophenyl)(1H-pyrazol-3-yl)methanone (5.0 g, 43.8% Yield) as a pale yellow oil. The crude product could be used next step without further purification. MS

m/z 357, 359 $[M+H]^+$.

Step 5. Methyl 2-((2-(benzyloxy)-4-bromophenyl)(1H-pyrazol-3-yl)methylene)hydrazine-1-carbodithioate

To a solution of (2-(benzyloxy)-4-bromophenyl)(1H-pyrazol-3-yl)methanone (2.5 g, 7.02 mmol) and methyl hydrazinecarbodithioate (1.7 g, 14.04 mmol)in EtOH (30 mL), was added CH_3COOH (0.1 mL) under N_2 was stirred at 80°C for 4h. The reaction solution was concentrated in vacuo to obtain a crude product methyl 2-((2-(benzyloxy)-4-bromophenyl)(1H-pyrazol-3-yl)methylene)hydrazine-1-carbodithioate (2.6g, 80.5% Yield) as a pale yellow oil, which is used directly for the next step. MS *m/z* 461, 463 $[M+H]^+$.

Step 6. 4-(2-(Benzyloxy)-4-bromophenyl)-7-(methylthio)pyrazolo[1,5-d][1,2,4]triazine

A solution of methyl 2-((2-(benzyloxy)-4-bromophenyl)(1H-pyrazol-3-yl)methylene)hydrazine-1-carbodithioate (2.6 g, 5.65 mmol) in Ph_2O(30 mL) was stirred at 170°C for 4h.The reaction mixture was cooled to room temperature. MeI (2.0 g, 14.12 mmol) and K_2CO_3 (1.95 g, 14.12mmol, 100 mass%) in THF (20 mL) and H_2O (10 mL) was then added to the mixture and the reaction mixture was stirred at rt for 2 h. 50 ml of water was then added. The mixture was extracted with EtOAc (2 x 80 mL). The organic layer was combined, dried over Na_2SO_4, evaporated in vacuo. The crude product was purified by silica gel chromatography (PE/EA=1/1) to afford desire product 4-(2-(benzyloxy)-4-bromophenyl)-7-(methylthio)pyrazolo[1,5-d][1,2,4]triazine(1.02g, 42.3% Yield) as a pale yellow solid. MS *m/z* 427.0, 429.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.35 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.38 (dd, J = 8.1, 1.8 Hz, 1H), 7.23 (ttd, J = 9.7, 4.9, 1.8 Hz, 5H), 6.97 (d, J = 2.2 Hz, 1H), 5.22 (s, 2H), 2.80 (d, J = 7.6 Hz, 3H).

Step 7. 4-(2-(Benzyloxy)-4-bromophenyl)-7-(methylsulfinyl)pyrazolo[1,5-d][1,2,4]triazine

To a solution of 4-(2-benzyloxy-4-bromo-phenyl)-7-methylsulfanyl-pyrazolo[1,5-d][1,2,4]triazine (50 mg, 0.12 mmol) in DCM (2 mL) was added m-CPBA (24.5 mg, 0.14 mmol,) at 0 °C under N_2. Then the reaction mixture was stirred at rt for 2 h. LCMS showed 15% starting materials was remained. m-CPBA(33 mg, 0.08 mmol) was added. The reaction mixture was stirred at rt for 2 h. 20 ml of saturated $NaHCO_3$ was added. The mixture was extracted with DCM (2 x 20 mL). The organic phase was dried over Na_2SO_4, evaporated in vacuum to give a

pale-yellow oil (45mg). The crude product could be used next step without further purification. MS *m/z* 443.1, 445.1 $[M+H]^+$.

Step 8. 4-(2-(Benzyloxy)-4-bromophenyl)-N-((3R,5R)-5-fluoro-1-methylpiperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-7-amine

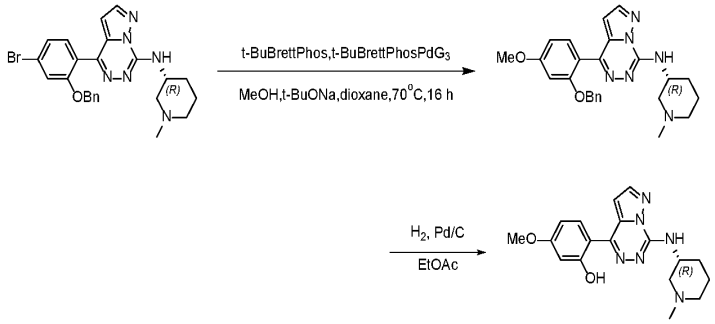
To a solution of 4-(2-benzyloxy-4-bromo-phenyl)-7-methylsulfinyl-pyrazolo[1,5-d][1,2,4]triazine (45 mg, 0.10 mmol) in DMSO (1 mL) was added (3R,5R)-5-fluoro-1-methyl-piperidin-3-amine hydrochloride (35 mg, 0.20 mmol) and DIEA (79 mg, 0.60 mmol) under N_2. Then the reaction mixture was stirred at rt for 16 h. Saturated aq. $NaHCO_3$ (20 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL). The organic layer was combined, dried over Na_2SO_4, and evaporated in vacuum. The crude product was purified by prep-HPLC (0.1%FA/H_2O:CH_3CN) 5% CH_3CN to 95% CH_3CN to give 19 mg of target compound. MS *m/z* 511.2, 513.2 $[M+H]^+$.

Step 9. 5-Bromo-2-(7-(((3R,5R)-5-fluoro-1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol

To a solution of 4-(2-(benzyloxy)-4-bromophenyl)-N-((3R,5R)-5-fluoro-1-methylpiperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-7-amine (40 mg,0.078mmol) in DCM (2 mL) was added BCl_3(1.0M solution in hexane) (0.5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. LCMS showed the reaction completed. MeOH (0.5mL) was slowly added under 0 °C and saturated $NaHCO_3$ (15 mL) was added. The mixture was extracted with DCM/MeOH=10:1 (2 x 20 mL), dried over Na_2SO_4, and evaporated in vacuum, The crude product was purified by prep-HPLC (0.1%FA/H_2O:CH_3CN) 5% CH_3CN to 95% CH_3CN to give 4.3 mg of target compound as a pale yellow solid. MS *m/z* 421.0, 423.0 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.27 (d, J = 2.0 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.21 – 7.10 (m, 2H), 4.99 (d, J = 46 Hz, 1H), 4.79 – 4.73 (m, 1H), 3.21 (d, J = 11.6 Hz, 1H), 3.02 (t, J = 11.6 Hz, 1H), 2.57-2.44 (m, 1H), 2.42 (s, 3H), 2.38-231 (m, 2H), 2.09-1.93 (m, 1H), NH and OH not observed.

Example 51

Preparation of Compound I-634



Step 1. (R)-4-(2-(Benzyloxy)-4-methoxyphenyl)-N-(1-methylpiperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-7-amine

The starting material, (R)-4-(2-(benzyloxy)-4-bromophenyl)-N-(1-methylpiperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-7-amine, was prepared in analogous manner according to the procedure of Example 50, using (R)-1-methylpiperidin-3-amine hydrochloride in place of (3R,5R)-5-fluoro-1-methyl-piperidin-3-amine hydrochloride in step 8.

To a solution of (R)-4-(2-(benzyloxy)-4-bromophenyl)-N-(1-methylpiperidin-3-yl)pyrazolo[1,5-d][1,2,4]triazin-7-amine (43 mg, 0.09 mmol) in dioxane (1 mL) was added t-BuBrettPhos (4.8 mg, 0.01 mmol,) t-BuBrettPhosPdG3(8.5mg, 0.01mmol), sodium tert-butoxide (26 mg, 0.27 mmol) and MeOH(29 mg, 0.9 mmol) under N_2.Then the reaction mixture was stirred at 70°C for 16h. Water (10 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The organic layer was combined, washed with brine, dried over Na_2SO_4, and evaporated in vacuum. The crude product was purified on silica gel eluted with (DCM/MeOH=20:1) to give the compound 4-(2-(benzyloxy)-4-bromophenyl)-7-(methylsulfinyl)pyrazolo[1,5-d][1,2,4]triazine (58 mg, 74.3% Yield) as a pale yellow oil. MS *m/z* 445.3 $[M+H]^+$.

Step 2. (R)-5-Methoxy-2-(7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol

To a solution of 4-(2-(benzyloxy)-4-bromophenyl)-7-(methylsulfinyl)pyrazolo[1,5-d][1,2,4]triazine (135 mg, 0.30 mmol) in EtOAc (3 mL) was added Pd/C(10%) (32 mg, 0.03 mmol) under N_2. Then the atmosphere was changed with H_2 three times. The reaction mixture was stirred at r.t. for 2 h, then filtered. The filtrate was concentrated under reduce pressure. The

crude was purified by Pre-HPLC (0.1%FA/H_2O:CH_3CN) to give (R)-5-methoxy-2-(7-((1-methylpiperidin-3-yl)amino)pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol (5.8 mg, 10.9% Yield) as a pale yellow solid. MS *m/z* 355.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.16 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.52 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 4.39-4.22 (m, 1H), 3.74 (s, 3H), 3.06-2.95 (m, 1H), 2.70-2.55 (m, 1H), 2.43-2.21 (m, 5H), 1.99-1.90 (m, 1H), 1.79 (dd, *J* = 9.5, 3.8 Hz, 1H), 1.70-1.55 (m, 2H), NH and OH not observed.

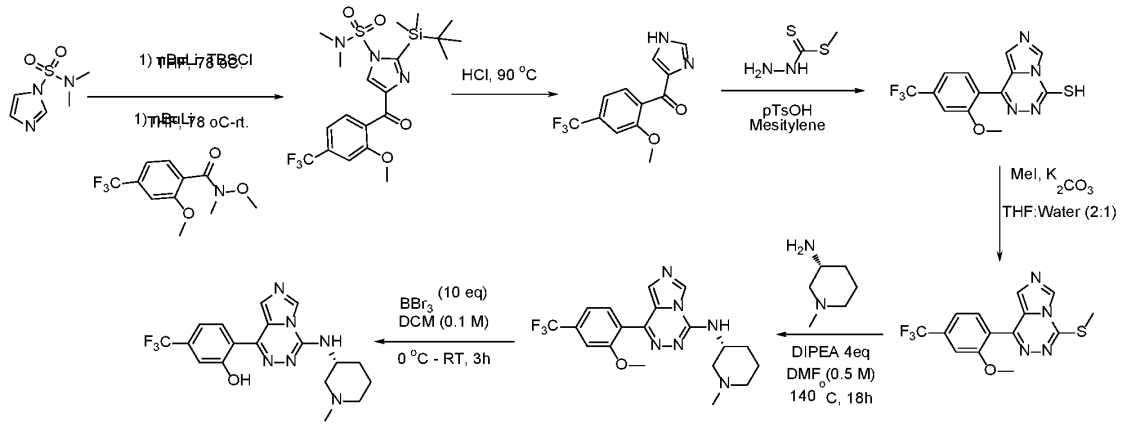
The compounds below were prepared according to the procedure of Example 50 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-390	MS *m/z* 403.0, 405.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 9.00 (d, J = 64 Hz, 2H), 8.28 (dd, J = 17.7, 5.2 Hz, 2H), 7.43 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.1, 1.6 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 4.74 – 4.43 (m, 1H), 3.87 (s, 1H), 3.80 (s, 3H), 3.52 (d, J = 10.4 Hz, 1H), 3.28 (d, J = 12.4 Hz, 1H), 3.11 (d, J = 10.0 Hz, 1H), 2.88 (d, J = 9.2 Hz, 1H), 2.09 (dd, J = 8.7, 3.6 Hz, 1H), 1.95 (dd, J = 18.0, 8.4 Hz, 1H), 1.90 – 1.72 (m, 2H).
I-391	MS *m/z* 390.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.42 (dd, J = 18.8, 4.7 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.21 (ddd, J = 10.2, 9.3, 1.9 Hz, 3H), 4.55 (s, 1H), 3.46 (d, J = 12.2 Hz, 2H), 3.20 (s, 1H), 3.06 – 2.96 (m, 1H), 2.83 (t, J = 10.8 Hz, 1H), 2.04 (s, 1H), 1.83 (ddd, J = 37.5, 24.7, 13.6 Hz, 3H).
I-451	MS *m/z* 417.0, 419.0$[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.31 (dd, J = 8.1, 1.5 Hz, 1H), 6.66 (d, J = 2.1 Hz, 1H), 4.71 – 4.51 (m, 1H), 3.83 (s, 3H), 3.70 – 3.56 (m, 1H), 3.30 (s, 1H), 3.02 (d, J = 22.7 Hz, 1H), 2.94 (s, 1H), 2.83 (s, 3H), 2.25 – 2.08 (m, 2H), 2.03 – 1.81 (m, 2H). NH not observed
I-452	MS *m/z* 403.0, 405.0$[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1H), 8.28 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.17 (dt, J = 8.3, 2.0 Hz, 2H), 4.50 (d, J = 4.0 Hz, 1H), 3.32 (s, 1H), 2.97 (s, 1H), 2.69 (d, J = 7.2 Hz, 1H), 2.65 – 2.49 (m, 4H), 2.13 (s, 1H), 1.98 (d, J = 4.8 Hz, 1H), 1.82 (dd, J = 14.0, 10.4 Hz, 2H). NH and OH not observed
I-453	MS *m/z* 417.1, 419.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.28 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.22 – 7.14 (m, 2H), 4.49 (s, 1H), 3.28 – 3.15 (m, 1H), 2.92 (s, 1H), 2.71 (q, J = 7.0 Hz, 2H), 2.62 (s, 2H), 2.11 (s, 1H), 1.94 (s, 1H), 1.81 (d, J = 10.0 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H). NH and OH not observed
I-544	MS *m/z*: 390.0, 392.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.28 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.41 – 6.97 (m, 3H), 4.47 – 4.16 (m, 1H), 2.92 – 2.42 (m, 2H), 2.31 (t, J = 10.1 Hz, 2H). NH and OH not observed
I-545	MS *m/z*: 493.0, 495.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.15 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 8.1, 1.7 Hz, 1H), 7.27 – 7.18 (m, 5H), 6.72 (d, J = 2.1 Hz, 1H), 5.15 (s, 2H), 4.65 – 4.54

Compound	Spectral Data
	(m, 1H), 3.64 (s, 1H), 3.32 – 3.27 (m, 1H), 3.04 (d, J = 86.1 Hz, 2H), 2.82 (s, 3H), 2.30 – 2.04 (m, 2H), 1.99 – 1.80 (m, 2H). NH and OH not observed
I-547	MS *m/z*: 390.0, 392.0 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.28 (d, J = 2.2 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.18 (dt, J = 8.4, 2.0 Hz, 2H), 4.35 (dd, J = 10.5, 6.5 Hz, 1H), 4.08 (dd, J = 11.1, 2.7 Hz, 1H), 3.83 (dd, J = 10.6, 5.6 Hz, 1H), 3.64 – 3.53 (m, 2H), 2.17 (s, 1H), 1.99 – 1.83 (m, 2H), 1.82 – 1.70 (m, 1H). NH and OH not observed
I-548	MS *m/z* 453.0, 455.0 $[M+H]^+$; ^1H NMR(400 MHz, MeOD) δ 8.28 (d,J = 2.2 Hz, 1H), 7.86 (d,J = 8.3 Hz, 1H), 7.28 (d,J = 2.2 Hz, 1H), 7.18 (dt,J = 8.3, 2.0 Hz, 2H), 6.01 (tt,J = 56.0, 4.3 Hz, 1H), 4.42 (s, 1H), 3.16 – 3.01 (m, 1H), 2.83 (td,J = 15.2, 4.3 Hz, 2H), 2.76 – 2.53 (m, 3H), 1.94 (s, 1H), 1.87 – 1.66 (m, 3H). NH and OH not observed
I-632	MS *m/z* 369.2 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.27 (d, J = 2.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 8.8, 2.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 4.60 – 4.46 (m, 1H), 3.84 (s, 3H), 3.70 – 3.57 (m, 1H), 3.36 (d, J = 6.8 Hz, 1H), 3.07 (q, J = 7.2 Hz, 2H), 3.00 – 2.77 (m, 2H), 2.25 – 2.06 (m, 2H), 2.00 – 1.80 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H). NH and OH not observed
I-633	MS *m/z* 353.3 $[M+H]^+$; ^1H NMR (400 MHz, MeOD) δ 8.17 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 4.40 (s, 1H), 3.40 – 3.28 (m, 1H), 3.04 – 2.93 (m, 1H), 2.76 (q, J = 7.0 Hz, 2H), 2.65 – 2.47 (m, 2H), 2.26 (s, 3H), 2.09 – 2.01 (m, 1H), 1.95 – 1.88 (m, 1H), 1.81 – 1.67 (m,2H), 1.15 (t, J = 7.2 Hz, 3H). NH and OH not observed

Example 52

Preparation of Compounds I-349 and I-333



Step 1: 1H-Imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone

A solution of N,N-dimethylimidazole-1-sulfonamide (5.17 g, 29.5 mmol) in tetrahydrofuran (0.3 M, 98 mL) was cooled to -78 °C. n-Butyllithium (2.5 mol/L) in hexanes (1.1

eq., 13 mL) was added slowly under argon. The reaction was stirred at the same temperature for 30 minutes. Then, tert-butyl-chloro-dimethyl-silane (1.1 eq., 4.89 g) in THF (<1 mL) was added dropwise. The reaction was allowed to warm up slowly to room temperature and continued to stir at room temperature for 10 minutes. The mixture was cooled to -78 °C and n-butyllithium (2.5 mol/L) in hexanes (1.1 eq., 13 mL) was added under argon. The reaction was warmed to -30 °C and stirred for 1 h. N,2-dimethoxy-N-methyl-4-(trifluoromethyl)benzamide (0.75 eq., 5.83 g, 22.1 mmol) was added and the reaction was warmed to room temperature and stirred for 3 hours. The reaction was quenched with ammonium chloride solution. The mixture was partitioned between sat. aq. ammonium chloride and EtOAc and extracted with EtOAc (x2). The organics were dried over Na_2SO_4 and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide 1H-imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone (7.0 g, 48% Yield). MS *m/z* 492.2 $[M+H]^+$

Step 2: 1H-Imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone

Hydrochloric acid (1 mol/L) in water (0.2 M, 71.2 ml) was added to 2-[tert-butyl(dimethyl)silyl]-4-[2-methoxy-4-(trifluoromethyl)benzoyl]-N,N-dimethyl-imidazole-1-sulfonamide (7 g, 14.21 mmol). The resulting mixture was warmed to 90°C and stirred for 1h. The crude material was cooled to room temperature and neutralized with 1 N NaOH to pH~7. The mixture was extracted with EtOAc (X4). Combined organics were dried over Na_2SO_4 and concentrated. The crude material was applied to the next step without future purification. MS *m/z* 271.2 $[M+H]^+$

Step 3: 1-[2-Methoxy-4-(trifluoromethyl)phenyl]imidazo[1,5-d][1,2,4]triazine-4-thiol

A mixture of 1H-imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone (3.0 g, 11 mmol), methyl N-aminocarbamodithioate (2 eq., 2.7 g, 22 mmol), p-toluenesulfonic acid (0.2 eq., 0.39 g, 2.2 mmol) and 1,3,5-trimethylbenzene (0.5 M, 22 mL,) was heated at 160 °C for 1 hour. The UPLC indicated the reaction in completed. The mixture was cooled to room temperature, then partitioned between brine and EtOAc, extracted with EtOAc (X5). Combined organics were dried over Na_2SO_4 and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide 1-[2-methoxy-4-(trifluoromethyl)phenyl]imidazo[1,5-d][1,2,4]triazine-4-thiol (2.9 g, 80% yield). MS *m/z* 327.1 $[M+H]^+$.

Step 4: 1-[2-Methoxy-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-imidazo[1,5-d][1,2,4]triazine

1-[2-Methoxy-4-(trifluoromethyl)phenyl]imidazo[1,5-d][1,2,4]triazine-4-thiol (3.2 g, 9.8 mmol) and potassium carbonate (2.5 g, 18 mmol) was mixed in tetrahydrofuran:water (2:1) (0.4 M, 25 mL). Then, iodomethane (2.5 g, 18 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between EtOAc and brine. After extraction, the organics were concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide 1-[2-methoxy-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-imidazo[1,5-d][1,2,4]triazine (2.43 g, 73% Yield). MS *m/z* 341.7 $[M+H]^+$.

Step 5: 1-[2-Methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]imidazo[1,5-d][1,2,4]triazin-4-amine

1-[2-Methoxy-4-(trifluoromethyl)phenyl]-4-methylsulfanyl-imidazo[1,5-d][1,2,4]triazine (150.0 mg, 0.4408 mmol) and (3R)-1-methylpiperidin-3-amine;trihydrochloride (2.0 eq., 0.19 g, 0.88 mmol) were mixed in N,N-diisopropylethylamine (10 eq., 0.76 mL, 4.4 mmol) and N,N-dimethylformamide (0.5 M, 0.8815 mL). The resulting mixture was warmed to 130 °C, and stirred for 15 h. After cooling, the crude material was directly loaded on silica column and purified, purified by flash column chromatography to afford 1-[2-methoxy-4-(trifluoromethyl) phenyl]-N-[(3R)-1-methyl-3-piperidyl]imidazo[1,5-d][1,2,4]triazin-4-amine (88 mg, 49.13% Yield). MS *m/z* 407.0 $[M+H]^+$. ^1H NMR (METHANOL-d4) δ: 8.62 (s, 1H), 8.51 (br s, 1H, formic acid peak), 7.44-7.66 (m, 1H), 7.34 (br s, 3H), 4.26-4.54 (m, 1H), 3.78 (s, 3H), 3.26 (br d, J=0.8 Hz, 1H), 2.75-2.97 (m, 1H), 2.45 (br s, 5H), 1.96-2.14 (m, 1H), 1.82-1.98 (m, 1H), 1.67-1.81 (m, 1H), 1.46-1.66 (m, 1H), NH and OH not observed.

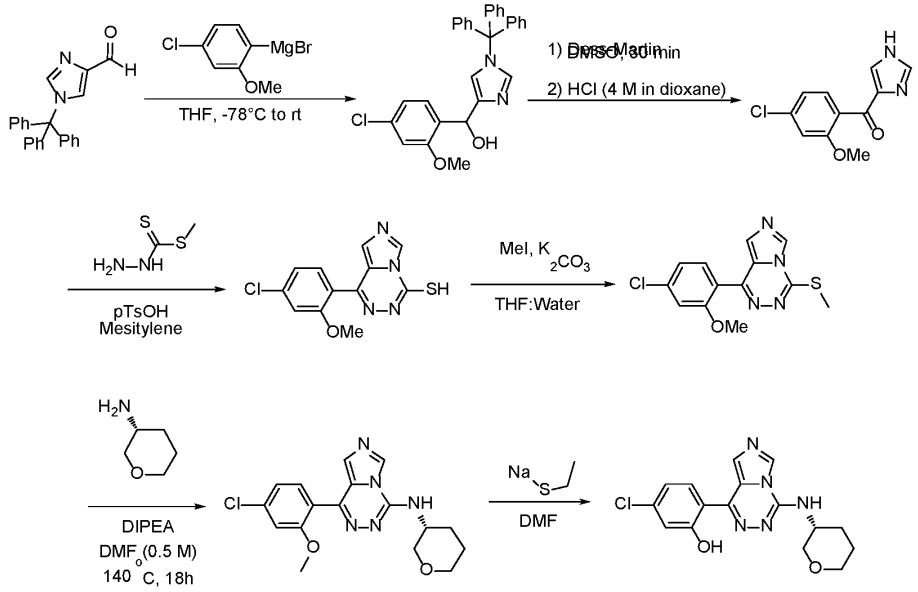
Step 6: 2-[4-[[(3R)-1-Methyl-3-piperidyl]amino]imidazo[1,5-d][1,2,4]triazin-1-yl]-5-(trifluoromethyl)phenol.

1-[2-Methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methyl-3-piperidyl]imidazo[1,5-d][1,2,4]triazin-4-amine (88 mg, 0.21 mmol) in dichloromethane (1.1 mL) was cooled to 0 ºC. Tribromoborane (10 eq., 0.2 mL, 2.2 mmol) was added and the resulting mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then cooled to 0 ºC and quenched with addition of K_2CO_3 and methanol carefully. After stirring for 30 minutes, the mixture was concentrated. The residue was then purified on prep-HPLC with 5-50% ACN in water with 0.1%

formic acid to provide 2-[4-[[(3R)-1-methyl-3-piperidyl]amino]imidazo[1,5-d][1,2,4]triazin-1-yl]-5-(trifluoromethyl)phenol (18 mg, 21 % Yield). MS *m/z* 393.1 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.73 (s, 1H), 8.10 (br s, 1H), 7.92-8.20 (m, 2H), 7.11-7.29 (m, 2H), 4.33-4.54 (m, 1H), 3.47-3.65 (m, 1H), 3.10-3.18 (m, 1H), 2.75-2.93 (m, 2H), 2.70 (s, 3H), 1.93-2.17 (m, 2H), 1.63-1.90 (m, 2H), NH and OH not observed.

Example 53

Preparation of Compound I-518



Step 1: (4-Chloro-2-methoxyphenyl)(1-trityl-1*H*-imidazol-4-yl)methanol

To a suspension of 1-trityl-1*H*-imidazole-4-carbaldehyde (5 g, 14.8 mmol, 1 eq.) in THF was added (4-chloro-2-methoxyphenyl)magnesium bromide (40 mL, 1.2 eq., 0.5 M in THF) dropwise at -78°C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Upon completion, the reaction was quenched with water and a white solid crashed out. The precipitate was filtered and dried under vacuum. The crude material was collected as (4-chloro-2-methoxyphenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (6.67 g, 94% yield) and was used in the next step without further purification.

Step 2. (4-Chloro-2-methoxyphenyl)(1*H*-imidazol-4-yl)methanone

(4-Chloro-2-methoxyphenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (1g, 2 mmol, 1 eq.,) was dissolved in minimum amount of DMSO, followed by addition of Dess-Martin reagents (2.2

g, 5.2 mmol, 2.5 eq.). The reaction was stirred at room temperature for 30 min. Then HCl (4 eq., 4 M in dioxane was added) to the reaction mixture slowly. The reaction was stirred at room temperature for another 30 min. Upon completion, the reaction was diluted with ethyl acetate and washed with DMSO. The organics were collected, dried over sodium sulphate, and concentrated under reduced pressure. The crude material was collected as (4-chloro-2-methoxyphenyl)(1*H*-imidazol-4-yl)methanone (372 mg, 76% yield) and was used in the next step without further purification. MS *m/z* 237.1, 239.1 $[M+H]^+$.

Steps 3 to 5.

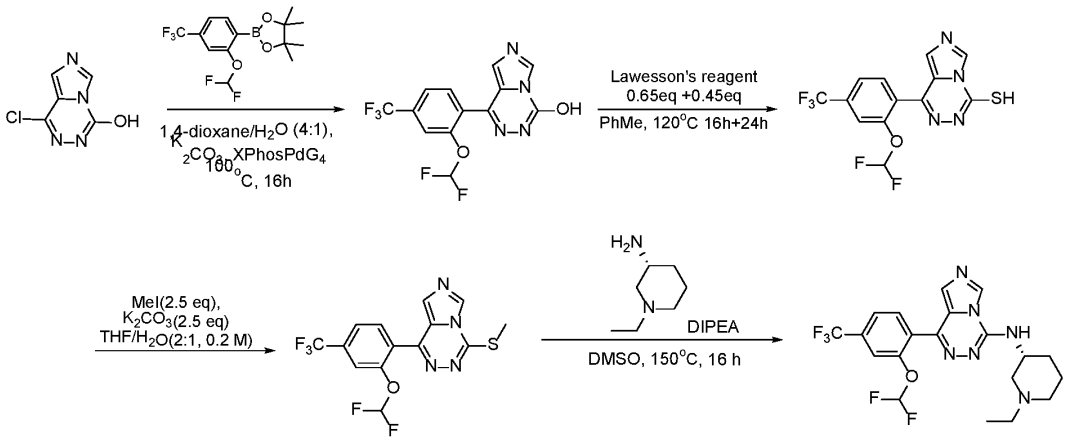
Intermediates in step 3 to 5 were prepared in analogous manner according to the procedure of Example 52, steps 3-5, using (4-chloro-2-methoxyphenyl)(1*H*-imidazol-4-yl)methanone in place of 1H-imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone in step 3, and using (R)-tetrahydro-2H-pyran-3-amine in place of (R)-1-methylpiperidin-3-amine in step 5.

Step 6. (R)-5-Chloro-2-(4-((tetrahydro-2H-pyran-3-yl)amino)imidazo[1,5-d][1,2,4]triazin-1-yl)phenol

To a vial was added 1-(4-chloro-2-methoxy-phenyl)-N-[(3*R*)-tetrahydropyran-3-yl]imidazo[1,5-*d*][1,2,4]triazin-4-amine (56 mg, 0.16 mmol, 1 eq.) and sodium ethanethiolate (73 mg, 0.8 mmol, 5 eq.), followed by DMF (0.5 M). The reaction was heated at 135 °C for 1 hour. Upon completion, the reaction was quenched with water and extracted with ethyl acetate. The organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column eluting with methanol (5% ammonia hydroxide) in DCM 0-5% to give 5-chloro-2-[4-[[(3*R*)-tetrahydropyran-3-yl]amino]imidazo[1,5-d][1,2,4]triazin-1-yl]phenol (45 mg, 83.6% yield). MS *m/z* 346.7, 348.4 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 9.11 (s, 1H), 8.16 (s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.08 – 7.01 (m, 2H), 4.21 – 4.10 (m, 1H), 4.08 – 4.00 (m, 1H), 3.81 – 3.73 (m, 1H), 3.51 – 3.37 (m, 2H), 2.19 – 2.10 (m, 1H), 1.89 – 1.74 (m, 2H), 1.74 – 1.59 (m, 1H). 1NH and 1 OH not observed.

Example 54

Preparation of Compound I-574



Step 1. 1-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)imidazo[1,5-d][1,2,4]triazin-4-ol

To a solution of 1-chloroimidazo[1,5-d][1,2,4]triazin-4-ol (Intermediate 3, 350 mg, 2.06 mmol) in dioxane/H_2O (4 mL/1mL) was added 2-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 7a, 1.04 g, 3.09 mmol), XPhos Pd-G4 (124 mg, 0.144 mmol) and K_2CO_3 (852 mg, 6.18 mmol). The mixture was stirred at 100°C for 3 h. After cooling to room temperature, the reaction was quenched with water (30 mL), extracted with EA (3x60 mL). The combined organic layers were concentrated in vacuo to get the crude product, which was purified by Pre-TLC (PE/EA=3:1) to provide the title compound as white solids (130 mg, yield 18.8%). LCMS $[M+H]^+$=347.0.

Step 2. 1-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)imidazo[1,5-d][1,2,4]triazine-4-thiol

A solution of methyl 1-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)imidazo[1,5-d][1,2,4]triazin-4-ol (130 mg, 0.375 mmol) in Toluene (5 mL) was added Phosphorus sulfide(83 mg, 0.375 mmol). The mixture was stirred at 120°C in a sealed tube for 24 h. After cooling to room temperature, it was concentrated in vacuo to get the crude product. The crude was purified by Pre-TLC (PE/EA=2:1) to provide the title compound as white solids (80 mg, yield 59%). MS *m/z* 363.1 $[M+H]^+$.

Step 3. 1-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-4-(methylthio)imidazo[1,5-d][1,2,4]triazine

To a solution of 1-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)imidazo[1,5-d][1,2,4]triazine-4-thiol (50 mg, 0.138 mmol) in THF/H_2O (4 mL/2 mL) was added Iodomethane (49 mg, 0.345 mmol) and K_2CO_3 (47 mg, 0.345 mmol). The mixture was stirred at rt for 30 mins. After that, the reaction was quenched with water (10 mL), extracted with EA (2 x 40 mL). The combined organic layers were concentrated in vacuo to provide the title compound which was used for next step without further purification (crude 50 mg). MS *m/z* 377.1 $[M+H]^+$.

Step 4. (R)-1-(2-(Difluoromethoxy)-4-(trifluoromethyl)phenyl)-N-(1-ethylpiperidin-3-yl)imidazo[1,5-d][1,2,4]triazin-4-amine

A solution of 1-(2-(difluoromethoxy)-4-(trifluoromethyl)phenyl)-4-(methylthio)imidazo[1,5-d][1,2,4]triazine (50 mg, 0.133 mmol) in DMSO (2 mL) was added (R)-1-ethylpiperidin-3-amine (43 mg, 0.332 mmol) and DIPEA (103 mg, 0.798 mmol). The mixture was stirred at 150°C in a sealed tube for 16 h. After cooling to room temperature, it was purified by Pre-HPLC to provide the title compound as white solids (11.2 mg, yield 17.8%). MS *m/z* 457.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.76 (s, 1H), 8.47 (s, 1H, formic acid), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 7.54 (s, 1H), 6.98 (t, *J* = 73.0 Hz, 1H), 4.61–4.41 (m, 1H), 3.79–3.54 (m, 1H), 3.29–3.24 (m, 1H), 3.11–3.00 (m, 2H), 2.95–2.72 (m, 2H), 2.27–2.07 (m, 2H), 1.96–1.77 (m, 2H), 1.32 (t, *J* = 7.3 Hz, 3H).

The compounds below were prepared according to the procedure of Example 54 by substituting the appropriate starting materials, reagents and reaction conditions.

Compound	Spectral Data
I-350	MS *m/z* 423.05 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.74 (s, 1H), 7.94-8.09 (m, 2H), 7.19-7.25 (m, 1H), 7.16 (s, 1H), 4.41-4.54 (m, 1H), 3.72-3.83 (m, 3H), 3.57-3.67 (m, 1H), 2.95-3.09 (m, 2H), 2.78-2.92 (m, 2H), 2.07-2.18 (m, 1H), 1.95-2.07 (m, 1H), 1.70-1.89 (m, 2H). NH and OH not observed.
I-360	MS *m/z* 407.4 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.74 (br s, 1H), 8.25 (br s, 1H, formic acid peak), 7.94-8.10 (m, 2H), 7.07-7.30 (m, 2H), 4.38-4.47 (m, 1H), 3.35-3.50 (m, 1H), 3.04 (br d, J=9.5 Hz, 1H), 2.71-2.87 (m, 2H), 2.53-2.65 (m, 2H), 2.10 (br d, J=10.5 Hz, 1H), 1.87-2.01 (m, 1H), 1.61-1.84 (m, 2H), 1.17 (t, J=7.3 Hz, 3H). NH and OH not observed.
I-383	MS *m/z* 373.8 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.61 (br s, 1H), 8.50 (br s, 1H, formic acid peak), 7.29-7.40 (m, 2H), 7.14 (s, 1H), 6.98 (s, 1H), 4.26-4.52 (m, 1H), 3.72 (s, 3H), 3.22-3.28 (m, 2H), 2.76-2.96 (m, 1H), 2.33-2.54 (m, 4H), 1.97-2.15 (m, 1H), 1.82-1.94 (m, 1H), 1.66-1.82 (m, 1H), 1.51-1.68 (m, 1H). NH and OH not observed.
I-384	MS m/z 359.0 $[M+H]^+$; ^1H NMR (METHANOL-d4) δ: 8.83 (s, 1H), 8.43 (br s, 1H, formic acid peak), 8.16 (br s, 1H), 7.96 (br d, J=6.4 Hz, 1H), 7.01-7.11 (m,

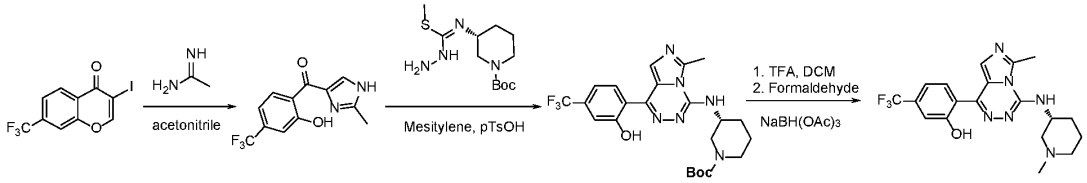
Compound	Spectral Data
	2H), 4.40-4.56 (m, 1H), 3.38-3.47 (m, 1H), 2.94-3.11 (m, 1H), 2.58 (m, 5H), 2.08-2.24 (m, 1H), 1.94-2.05 (m, 1H), 1.80-1.91 (m, 1H), 1.64-1.78 (m, 1H). NH and OH not observed.
I-397	MS *m/z* 380.2 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.77-9.01 (m, 1H), 8.08-8.25 (m, 2H), 7.22-7.39 (m, 2H), 4.28-4.47 (m, 1H), 4.12-4.26 (m, 1H), 3.82-3.99 (m, 1H), 3.43-3.67 (m, 2H), 2.19-2.35 (m, 1H), 1.78-1.95 (m, 3H). NH and OH not observed.
I-435	MS *m/z* 345.4 $[M+H]^+$; ^{1}H NMR (METHANOL-d_4) δ: 8.85 (s, 1H), 8.15 (s, 1H), 7.89-7.99 (m, 1H), 7.05 (br s, 2H), 4.42-4.65 (m, 1H), 3.82 (m, 2H), 3.39-3.49 (m, 1H), 3.13 (m, 1H), 2.26-2.35 (m, 1H), 2.19 (m, 2H), 1.89-1.99 (m, 2H). NH and OH not observed.
I-436	MS *m/z* 389.3 $[M+H]^+$; ^{1}H NMR (DMSO-d6) δ: 8.84-9.03 (m, 1H), 8.11-8.27 (m, 1H), 7.95-8.05 (m, 1H), 7.08 (br s, 2H), 4.33-4.50 (m, 1H), 4.21-4.31 (m, 1H), 3.53 (br s, 2H), 3.17 (br s, 2H), 2.84 (br s, 1H), 1.94-2.21 (m, 3H), 1.77 (br d, J=6.0 Hz, 1H), 1.53-1.67 (m, 1H), 1.35-1.52 (m, 1H). NH and OH not observed.
I-442	MS *m/z* 371.2 $[M-H]^-$; ^{1}H NMR (METHANOL-d4) δ: 8.69 (s, 1H), 8.34 (br s, 1H, formic acid peak), 8.02 (br s, 1H), 7.81 (br s, 1H), 6.79-7.05 (m, 2H), 4.37 (br s, 1H), 3.37 (br d, J=8.9 Hz, 1H), 2.89-3.09 (m, 1H), 2.71 (br d, J=5.4 Hz, 2H), 2.28-2.55 (m, 2H), 2.00-2.19 (m, 1H), 1.82-1.98 (m, 1H), 1.67-1.81 (m, 1H), 1.50-1.67 (m, 1H), 1.14 (br t, J=7.1 Hz, 3H). NH and OH not observed.
I-460	MS *m/z* 391.3 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.82 (br s, 1H), 8.44 (br s, 1H, formic acid peak), 8.15 (br s, 2H), 7.29 (br s, 2H), 5.96-6.18 (m, 2H), 4.95-5.14 (m, 1H), 3.09-3.24 (m, 2H), 2.95-3.06 (m, 1H), 2.58 (s, 3H), 2.45 (s, 1H). NH and OH not observed.
I-512	MS *m/z* 394.3 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.81 (s, 1H), 7.99 (br s, 2H), 7.22 (s, 2H), 4.14-4.36 (m, 1H), 3.66-3.93 (m, 1H), 3.25—3.36 (m, 2H), 3.002-3.11 (m, 1H), 2.41-2.59 (m, 1H), 2.12-2.22 (m, 1H), 1.99-2.07 (m, 1H), 1.85-1.96 (m, 1H), 1.41-1.55 (m, 1H). NH and OH not observed.
I-527	MS *m/z* 380.2 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.73-8.87 (m, 1H), 8.02-8.19 (m, 2H), 7.24-7.30 (m, 1H), 7.20 (br s, 1H), 4.14-4.37 (m, 1H), 2.67 (m, 2H), 2.26-2.33 (m, 2H), 1.46 (s, 3H). NH and OH not observed.
I-528	MS *m/z* 411.3 $[M+H]^+$; ^{1}H NMR (METHANOL-d4) δ: 8.69 (s, 1H), 8.44 (br s, 1H, formic acid peak), 7.99-8.10 (m, 2H), 7.16 (s, 2H), 4.84-5.05 (m, 1H), 4.61-4.70 (m, 1H), 3.24-3.32 (m, 1H), 2.95-3.10 (m, 1H), 2.34 (s, 5H), 2.14-2.27 (m, 1H), 1.68-1.97 (m, 1H). NH and OH not observed.
I-549	MS *m/z* 346.6, 348.4 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 8.15 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.09 – 6.96 (m, 2H), 4.24 (p, J = 8.3 Hz, 1H), 2.73 – 2.64 (m, 2H), 2.34 – 2.25 (m, 2H), 1.47 (s, 3H). 2OH and 1NH are not observed.
I-553	MS *m/z* 387.7, 389.0 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 8.11 (s, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.07 – 7.02 (m, 2H), 4.69 – 4.50 (m, 1H), 3.87 – 3.72 (m, 1H), 3.62 – 3.51 (m, 1H), 3.48 – 3.38 (m, 1H), 3.15 – 2.86 (m,

Compound	Spectral Data
	2H), 2.38 – 2.17 (m, 2H), 2.09 – 1.77 (m, 2H), 1.40 (d, J = 3.6 Hz, 6H). NH and OH not observed
I-557	MS *m/z* 377.2, 379.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.78 (s, 1H), 8.21 (s, 1H, formic acid peak), 8.15 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.09 – 7.02 (m, 2H), 5.26 – 4.96 (m, 1H), 4.84 – 4.66 (m, 1H), 3.69 – 3.47 (m, 1H), 2.82 – 2.42 (m, 7H), 2.19 – 1.76 (m, 1H). NH and OH not observed.
I-558	MS *m/z* 427.3, 429.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.15 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.19 – 6.87 (m, 2H), 4.46 – 4.24 (m, 1H), 3.27 – 3.15 (m, 3H), 3.04 – 2.88 (m, 1H), 2.63 – 2.45 (m, 2H), 2.27 – 2.11 (m, 1H), 1.97 – 1.72 (m, 2H), 1.68 – 1.49 (m, 1H). 1NH and 1 OH not observed
I-559	MS *m/z* 409.3, 411.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.15 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.04 (t, 1H), 4.49 – 4.20 (m, 1H), 3.04 – 2.74 (m, 3H), 2.56 – 2.34 (m, 2H), 2.29 – 2.07 (m, 1H), 1.96 – 1.67 (m, 2H), 1.66 – 1.49 (m, 1H). NH and OH not observed. 1H under solvent peak
I-561	MS *m/z* 332.1, 334.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 13.66 (s, 1H), 8.97 (s, 1H), 8.54 – 8.09 (m, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.23 – 6.83 (m, 2H), 4.95 – 4.51 (m, 1H), 4.14 – 3.91 (m, 2H), 3.90 – 3.70 (m, 2H), 2.41 – 2.27 (m, 1H), 2.15 – 2.03 (m, 1H).
I-578	MS *m/z* 360.2, 362.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.08 – 7.02 (m, 2H), 4.32 – 4.13 (m, 1H), 3.95 – 3.62 (m, 1H), 2.80 – 2.42 (m, 1H), 2.35 – 2.14 (m, 1H), 2.13 – 1.98 (m, 1H), 1.98 – 1.80 (m, 1H), 1.67 – 1.09 (m, 4H). 1NH and 2 OH not observed.
I-580	MS *m/z* 330.2, 332.1 $[M-H]^-$; ^1H NMR (400 MHz, CD_3OD) δ 8.87 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.23 – 6.86 (m, 2H), 4.84 – 4.76 (m, 1H), 4.17 – 4.03 (m, 2H), 4.01 – 3.85 (m, 2H), 2.47 (m, 1H), 2.20 (m, 1H). 1NH and 1OH not observed
I-581	MS *m/z* 372.2, 374.2 $[M-H]^-$; ^1H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.33 – 6.71 (m, 2H), 4.20 (s, 1H), 3.47 – 3.41 (m, 4H), 2.66 – 2.53 (m, 1H), 2.29 – 2.10 (m, 2H), 2.01 – 1.89 (m, 1H), 1.70 – 1.17 (m, 4H). NH and OH not observed.
I-623	MS *m/z*: 433.1, 435.1 $[M+H]^+$; ^1H NMR (400 MHz,CD_3OD) δ 8.81 (s, 1H), 8.44 (s, 1H, formic acid proton), 8.10 (s, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.24 – 7.10 (m, 2H), 4.60 – 4.37 (m, 1H), 3.80 (t, J = 5.5 Hz, 2H), 3.56 – 3.42 (m, 1H), 3.16 – 3.02 (m, 1H), 2.99 – 2.83 (m, 2H), 2.81 – 2.61 (m, 2H), 2.20 – 2.07 (m, 1H), 2.06 – 1.96 (m, 1H), 1.92 – 1.71 (m, 2H). NH and OH not observed
I-624	MS *m/z*: 443.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.43 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.52 (s, 1H), 6.98 (t, J = 73.0 Hz, 1H), 4.60 – 4.43 (m, 1H), 3.71 – 3.52 (m, 1H), 3.29 – 3.22 (m, 1H), 3.19 – 2.91 (m, 2H), 2.83 (s, 3H), 2.26 – 2.06 (m, 2H), 2.00 – 1.75 (m, 2H). NH and OH not observed
I-625	MS *m/z*: 461.1 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68 (s, 1H), 7.54 (s, 1H), 6.96 (t, J = 73.0 Hz, 1H), 5.12 – 5.07 (m, 1H), 3.58 – 3.48 (m, 1H), 3.37 – 3.32 (m, 1H),

Compound	Spectral Data
	2.85 – 2.70 (m, 1H), 2.65 (s, 1H), 2.61 (s, 3H), 2.59 – 2.45 (m, 2H), 2.07 – 1.88 (m, 1H). NH and OH not observed
I-626	MS *m/z*: 371.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 7.44 (s, 1H), 6.63 (s, 1H), 6.60 (d, J = 11.0 Hz, 1H), 4.51 – 4.35 (m, 1H), 3.24 (dd, J = 10.4, 5.0 Hz, 1H), 2.90 – 2.75 (m, 1H), 2.56 (dt, J = 7.3, 4.6 Hz, 2H), 2.34 (s, 3H), 2.33 – 2.21 (m, 2H), 2.14 (dd, J = 9.4, 3.7 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.76 (ddd, J = 17.5, 12.3, 8.5 Hz, 1H), 1.63 (d, J = 10.6 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H). NH and OH not observed
I-627	MS *m/z*: 390.2, 392.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.94 (s, 1H), 8.17 (s, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.23 (m, 2H), 4.20 (p, J = 7.9 Hz, 1H), 2.70 – 2.63 (m, 2H), 2.32 (dd, J = 11.0, 9.1 Hz, 2H), 1.44 (s, 3H). NH and OH not observed
I-628	MS *m/z*: 417.2, 419.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.78 (s, 1H), 8.11 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.18 (m, 2H), 4.58 – 4.45 (m, 1H), 3.81 – 3.66 (m, 1H), 3.45 – 3.34 (m, 1H), 3.07 (dd, J = 14.0, 6.9 Hz, 2H), 2.97 – 2.71 (m, 2H), 2.30 – 2.20 (m, 1H), 2.17 – 2.08 (m, 1H), 1.98 – 1.78 (m, 2H), 1.32 (t, J = 7.3 Hz, 3H). NH and OH not observed.

Example 55

Preparation of Compound I-543



Step 1: (2-Hydroxy-4-(trifluoromethyl)phenyl)(2-methyl-1H-imidazol-4-yl)methanone

3-Iodo-7-(trifluoromethyl)-4H-chromen-4-one (2.34 g, 6.89 mmol), acetamidine hydrochloride (0.97 g, 2.4 eq.) and potassium carbonate (2.85 g, 3 eq.) was mixed in 2-amino-3-chloro-1,4-naphthoquinone (25 mL). The resulting mixture was warmed to 80 °C, and stirred for 1 h. Solvent was removed and the crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide (2-hydroxy-4-(trifluoromethyl)phenyl)(2-methyl-1H-imidazol-4-yl)methanone (1.04 g, 55% yield). MS *m/z* 271.2 $[M+H]^+$.

Step 2. (R)-2-(6-Methyl-4-(piperidin-3-ylamino)imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

To a solution of (2-hydroxy-4-(trifluoromethyl)phenyl)(2-methyl-1H-imidazol-4-

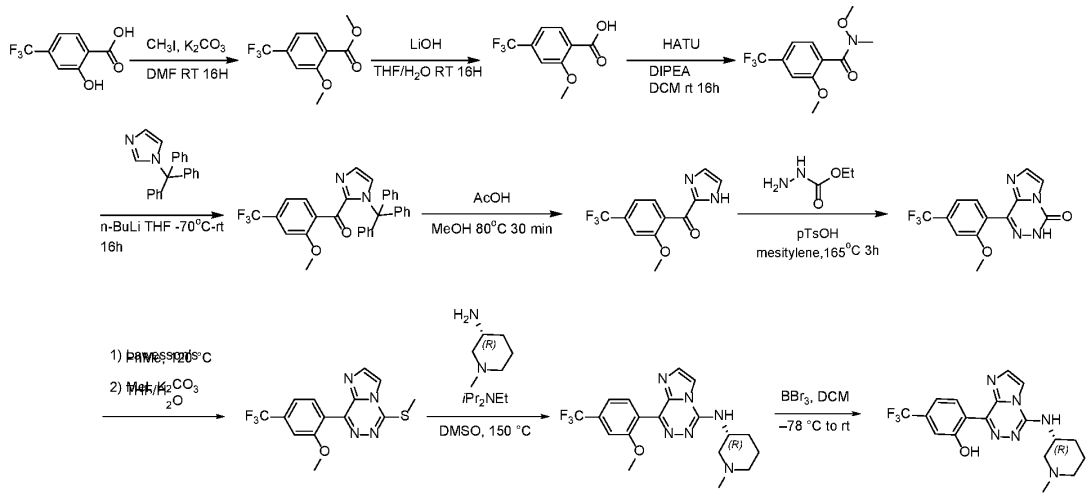
yl)methanone (828 mg, 3.06 mmol) in ethanol (9 mL) was added tert-butyl (3R)-3-[(E)-[hydrazino(methylsulfanyl)methylene]amino]piperidine-1-carboxylate (1.78 g, 2.1 eq.) and acetic acid (0.5 mL, 3.0 eq.). The resulting mixture was warmed to 80°C and stirred for 1 h. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was neutralized to pH ~ 6-7, then extracted with EtOAc (X5). The organics were concentrated and the crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide tert-butyl (R)-3-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)-6-methylimidazo[1,5-d][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate (438 mg, 29 % yield). MS *m/z* 493.2 $[M+H]^+$.

Step 3: (R)-2-(6-Methyl-4-((1-methylpiperidin-3-yl)amino)imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

Deprotection of tert-butyl (R)-3-((1-(2-hydroxy-4-(trifluoromethyl)phenyl)-6-methylimidazo[1,5-d][1,2,4]triazin-4-yl)amino)piperidine-1-carboxylate followed by reductive N-methylation according to procedure of Example 49, step 4 to provide (R)-2-(6-methyl-4-((1-methylpiperidin-3-yl)amino)imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol: MS *m/z*: 407.1 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H, formic acid proton), 7.89 (s, 1H), 7.64 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.23 (s, 1H), 4.42 – 3.88 (m, 1H), 3.15 – 3.05 (m, 1H), 3.02 (s, 3H), 2.86 – 2.56 (m, 3H), 2.51 (s, 3H), 2.04 – 1.90 (m, 2H), 1.85 – 1.61 (m, 2H). NH and OH not observed.

Example 56

Preparation of Compounds I-386 and I-398



Step 1. Methyl 2-methoxy-4-(trifluoromethyl)benzoate

To a solution of 2-hydroxy-4-(trifluoromethyl) benzoic acid (32.0 g, 155 mmol, 1.0 eq.) and K_2CO_3 (64.0 g, 465 mmol, 3.0 eq.) in DMF (320 mL, 0.5 M) was added iodomethane (55.0 g, 387 mmol, 2.5 eq.) at 0°C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was diluted with water and extracted with EA. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain methyl 2-methoxy-4-(trifluoromethyl) benzoate (36.0 g, 154 mmol, 99% yield) as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.85 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.20 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H).

Step 2. 2-Methoxy-4-(trifluoromethyl)benzoic acid

To a solution of methyl 2-methoxy-4-(trifluoromethyl) benzoate (36.0 g,153 mmol, 1.0 eq.) in tetrahydrofuran and methanol (300 mL, 1:1) was added lithium hydroxide (9.60 g, 229 mmol, 1.5 eq.) at room temperature. The reaction mixture was stirred at room temperature for 16 hours and then the solvent was removed. The residue was dissolved in water, acidified with hydrochloric acid (1M) and extracted with EA (200 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 2-methoxy-4-(trifluoromethyl) benzoic acid (28.4 g, 129 mmol, 84.3% yield) as a white solid,

which was used to the next step without purification. MS *m/z* 221.1 $[M+H]^+$.

Step 3. *N*,2-Dimethoxy-N-methyl-4-(trifluoromethyl)benzamide

To a solution of 2-methoxy-4-(trifluoromethyl) benzoic acid (28.4 g, 129 mmol, 1.0 eq.) in DCM (300 mL, 0.4 M) were added HATU (58.9 g, 155 mmol, 1.2 eq.), DIPEA (50.0 g, 387 mmol, 3.0 eq.) and N,O-dimethylhydroxylamine hydrochloride (15.0 g, 155 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature for 16 h. Upon completion, the mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 400 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain *N*,2-dimethoxy-N-methyl-4-(trifluoromethyl) benzamide (33.7 g, 128.1 mmol, yield 99%) as a colorless oil. MS *m/z* 264.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 7.49 (d, J = 7.8 Hz, 1H), 7.39 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 3.90 (s, 3H), 3.45 (s, 3H), 3.27 (s, 3H).

Step 4. (2-Methoxy-4-(trifluoromethyl) phenyl) (1-trityl-1H-imidazol-2-yl)methanone

To a solution of 1-trityl-1H-imidazole (3.72 g, 12.0 mmol, 1.0 eq.) in THF (60 mL) was added n-BuLi (7.5 mL, 1.6 M in THF, 12.0 mmol, 1.0 eq.) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, then *N*,2-dimethoxy-N-methyl-4-(trifluoromethyl) benzamide (2.63 g, 10.0 mmol, 0.8 eq.) was added. The reaction mixture warmed to room temperature and stirred for 16 h. Upon completion, the mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain (2-methoxy-4-(trifluoromethyl) phenyl) (1-trityl-1H-imidazol-2-yl)methanone (374 mg, yield 6.1%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ: 7.33 – 7.27 (m, 9H), 7.22 – 7.10 (m, 10H), 7.06 (s, 1H), 3.75 (s, 3H).

Step 5. (1H-Imidazol-2-yl) (2-methoxy-4-(trifluoromethyl)phenyl)methanone

A mixture of (2-methoxy-4-(trifluoromethyl) phenyl) (1-trityl-1H-imidazol-2-yl)methanone (1.88 g, 3.60 mmol, 1.0 eq.) in 5% acetic acid/methanol solution (126 mL) was heated to reflux for 0.5 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain (1H-imidazol-2-yl) (2-methoxy-4-(trifluoromethyl) phenyl)methanone (825 mg, yield 84.8%) as a white solid. MS *m/z* 271.1 $[M+H]^+$, ^1H NMR (400

MHz, Chloroform-*d*) δ: 10.65 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.35 – 7.32 (d, J = 9.2 Hz, 2H), 7.29 (d, J = 1.4 Hz, 1H), 7.22 (s, 1H), 3.88 (s, 3H).

Step 6. 8-(2-Methoxy-4-(trifluoromethyl) phenyl) imidazo[1,2-d] [1,2,4] triazin-5(6H)-one

To a solution of (1H-imidazol-2-yl)(2-methoxy-4-(trifluoromethyl)phenyl)methanone (825 mg, 3.00 mmol, 1.0 eq.) in 1,3,5-trimethyl-benzene (80 mL, 0.04 M) was added toluene-4-sulfonic acid (58 mg, 0.300 mmol, 0.1 eq.) and ethyl hydrazinecarboxylate (476 mg, 4.50 mmol, 1.5 eq.). After stirring at 165° C for 3 h, the mixture was cooled to room temperature and diluted with EA (150 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 0% ~ 30%) to obtain 8-(2-methoxy-4-(trifluoromethyl) phenyl) imidazo[1,2-d] [1,2,4] triazin-5(6H)-one (295 mg, yield 31.7%) as a white solid. MS *m/z* 311.0 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d6) δ: 13.13 (s, 1H), 8.11 (d, J = 1.4 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H).

Step 7. 8-[2-Methoxy-4-(trifluoromethyl)phenyl]-6*H*-imidazo[1,2-*d*][1,2,4]triazine-5-thione

A suspension of 8-[2-methoxy-4-(trifluoromethyl)phenyl]-6*H*-imidazo[1,2-*d*][1,2,4]triazin-5-one (0.195 g, 0.629 mmol) in PhMe (2.5 mL) was added Lawesson's reagent (0.183 g, 0.440 mmol). The mixture was heated to 120 °C. The reaction cooled to rt and diluted with EtOAc. The solution was washed with water, sat. $NaHCO_3$, brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:DCM, 0 to 20%) gave a white solid (0.117 g, 57%). MS *m/z* 327.3 $[M+H]^+$.

Step 8. 8-[2-Methoxy-4-(trifluoromethyl)phenyl]-5-methylsulfanyl-imidazo[1,2-*d*][1,2,4]triazine

A solution of 8-[2-methoxy-4-(trifluoromethyl)phenyl]-6*H*-imidazo[1,2-*d*][1,2,4]triazine-5-thione (0.189 g, 0.579 mmol) in THF/H_2O (2:1, 1.5 mL) was added MeI (65 mL, 1.04 mmol) and K_2CO_3 (0.144 g, 1.04 mmol). The mixture was stirred at rt for 40 min. The reaction was diluted with EtOAc, washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by chromatography on SiO_2 (EtOAc:hexanes, 5-60%) gave a white solid (0.158 g, 80%). MS *m/z* 341.3 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.02 (s, 1 H), 7.87 (s, 1 H), 7.71 (d, *J* = 7.40 Hz, 1 H), 7.50 – 7.42 (m, 2 H), 3.84 (s, 3 H), 2.96 (s, 3 H).

Step 9. 8-[2-Methoxy-4-(trifluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]imidazo[1,2-*d*][1,2,4]triazin-5-amine formic acid salt

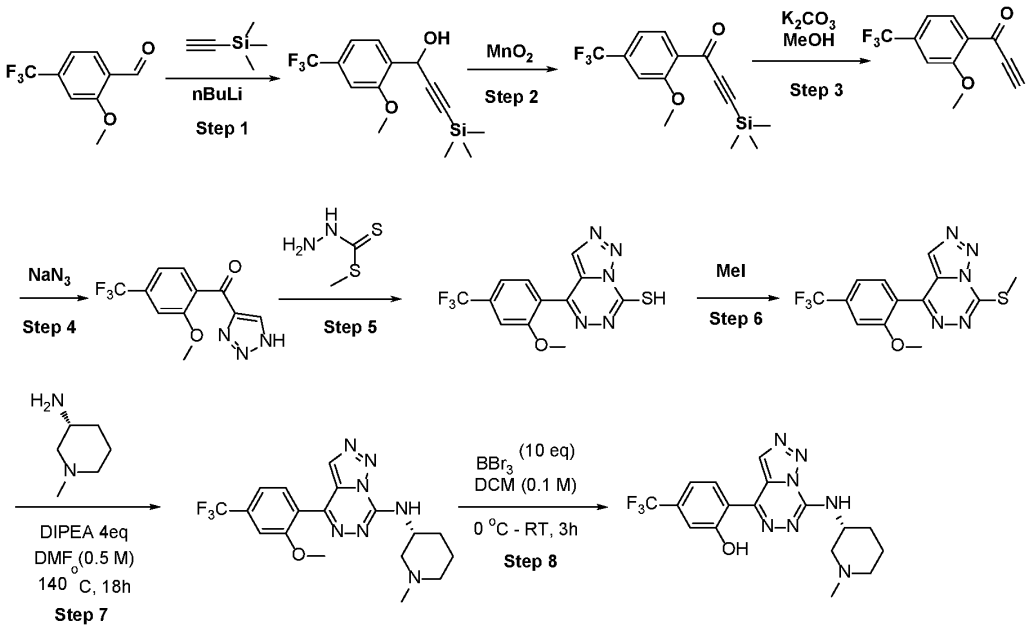
A mixture of 8-[2-methoxy-4-(trifluoromethyl)phenyl]-5-methylsulfanyl-imidazo[1,2-*d*][1,2,4]triazine (0.095 g, 0.280 mmol) and (3*R*)-1-methylpiperidin-3-amine (0.080 g, 0.700 mmol) in DMSO (0.37 mL) and *i*Pr$_2$NEt (0.15 mL, 0.840 mmol) was heated to 150 °C for 20 h. The reaction was cooled to rt and diluted with DCM/iPrOH (9:1). The solution was washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a tan solid (0.069 g, 55%). MS *m/z* 407.1 $[M+H]^+$; ^{1}H NMR (500 MHz, CD_3OD) δ 8.45 (s, 1H, formic acid), 8.14 (s, 1H), 7.75 (s, 1H), 7.63 (d, *J* = 8.09 Hz, 1H), 7.45 – 7.40 (m, 2H), 4.61 – 4.49 (m, 1H), 3.82 (s, 3H), 3.64 – 3.49 (m, 1 H), 3.20 – 3.10 (m, 1H), 2.76 – 2.63 (m, 5H), 2.29 – 2.14 (m, 1H), 2.11 – 2.00 (m, 1H), 1.95 – 1.71 (m, 2H). NH not observed.

Step 10. 2-[5-[[(3*R*)-1-Methyl-3-piperidyl]amino]imidazo[1,2-*d*][1,2,4]triazin-8-yl]-5-(trifluoromethyl)phenol formic acid salt

A solution of 8-[2-methoxy-4-(trifluoromethyl)phenyl]-*N*-[(3*R*)-1-methyl-3-piperidyl]-imidazo[1,2-*d*][1,2,4]triazin-5-amine (0.087 g, 0.21 mmol) in DCM (0.80 mL) was cooled to –78 °C. BBr_3 (1.0 M in DCM, 2.1 mL, 2.1 mmol) was added and the reaction stirred at –78 °C for 20 min before warming to rt. After 1.5 h, the reaction was quenched by slowly adding the reaction mixture to a stirred solution of DCM/MeOH (10:1, 11 mL). Sat. $NaHCO_3$ was then added, and the mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on SiO_2 (MeOH:DCM, 0 to 10%) followed by reverse phase chromatography (0.1% formic acid in MeCN:0.1% formic acid in H_2O, 5 to 100%) gave a tan solid (0.040 g, 43%). MS *m/z* 393.4 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (d, *J* = 8.4 Hz, 1H), 8.44 (s, 1H), 8.20 – 8.00 (m, 2H, including formic acid), 7.96 (s, 1H), 7.35 (br d, *J* = 8.5 Hz, 1H), 7.28 (s, 1H), 4.36 – 4.27 (m, 1H), 3.08 (d, *J* = 8.1 Hz, 1H), 2.73 (br d, *J* = 11.1 Hz, 1H), 2.24 (s, 3H), 2.08 – 1.92 (m, 3H), 1.84 – 1.73 (m, 1H), 1.67 – 1.55 (m, 1H), 1.51 – 1.40 (m, 1H). 1H not observed (OH).

Example 57

Preparation of Compound I-461



Step 1: 1-[2-Methoxy-4-(trifluoromethyl) phenyl]-3-trimethylsilyl-prop-2-yn-1-ol

To a solution of ethynyl(trimethyl)silane (2.65 g, 1.1 eq., 27 mmol) in tetrahydrofuran (0.25 M) was added n-butyllithium (in hexanes, 1.05 eq., 26 mmol, 2.5 M) dropwise at -78 °C. The resulting mixture was stirred at -78°C for 1 hour, followed by addition of a solution of 2-methoxy-4-(trifluoromethyl) benzaldehyde (5.0 g, 24 mmol) in THF (5 mL) dropwise. The reaction was then warmed to 0 °C. After stirring at 0 °C for 20 minutes, ammonium chloride solution was added and the reaction was diluted with EtOAc. The organics were washed with water, sat. NaHCO3, brine, dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash column chromatography on silica gel eluting with 0-50% EtOAc in hexane to provide 1-[2-methoxy-4-(trifluoromethyl) phenyl]-3-trimethylsilyl-prop-2-yn-1-ol (6.7 g, 90% Yield).

Step 2. 1-[2-Methoxy-4-(trifluoromethyl) phenyl]-3-trimethylsilyl-prop-2-yn-1-one

A mixture of 1-[2-methoxy-4-(trifluoromethyl) phenyl]-3-trimethylsilyl-prop-2-yn-1-ol (6.7 g, 22 mmol) and manganese dioxide (5 eq., 110 mmol) in dichloromethane (0.2 M) was stirred at room temperature for 4 h. The crude material was passed through a celite pad and washed with DCM. The organic volatiles were removed, and the crude material was used for the

next step without purification.

Step 3: 1-[2-Methoxy-4-(trifluoromethyl) phenyl]-3-H-prop-2-yn-1-one

A mixture of 1-[2-methoxy-4-(trifluoromethyl) phenyl]-3-trimethylsilyl-prop-2-yn-1-one (6.7 g, 22 mmol) and potassium carbonate (5 eq., 110 mmol) in methanol (0.2 M) was stirred at room temperature for 20 minutes. The crude material was passed through a celite pad and the organic volatiles were removed. The crude material was concentrated down and loaded on the column for purification eluting with hexane/ EtOAc (0-50%) to afford 1-[2-methoxy-4-(trifluoromethyl) phenyl]prop-2-yn-1-one (2.1 g, 41% Yield).

Step 4. [2-Methoxy-4-(trifluoromethyl) phenyl] -(1H-triazol-4-yl)methanone

A suspension of sodium azide (4 eq., 2.4 g, 37 mmol) in DMSO (0.3 M, 31 mL) was heated to 90 °C. A solution of 1-[2-methoxy-4-(trifluoromethyl) phenyl] prop-2-yn-1-one (750 mg, 0.75 g, 3.28 mmol) in DMSO (10 ml) was added dropwise. The resulting mixture was continued to stir at 90 °C for 4h. After cooling, the reaction was poured into ice/HCl (aq.), then extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 0-100% EtOAc in hexane to provide [2-methoxy-4-(trifluoromethyl) phenyl]-(1H-triazol-4-yl)methanone (460 mg, 18% Yield). MS *m/z* 272.0 $[M+H]^+$

Step 5-8: **(R)-2-(7-((1-Methylpiperidin-3-yl)amino)-[1,2,3]triazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol**

The title compound was prepared, as formic acid salt, in analogous manner according to the procedure of Example 52, steps 3-6, using [2-methoxy-4-(trifluoromethyl) phenyl]-(1H-triazol-4-yl)methanone in place of 1H-imidazol-4-yl-[2-methoxy-4-(trifluoromethyl)phenyl]methanone in step 3.MS *m/z* 394.3 $[M+H]^+$; ^1H NMR (CD_3OD) δ: 8.81 (s, 1H), 8.47 (br s, 1H, formic acid peak), 8.07-8.19 (m, 1H), 7.32 (br s, 2H), 4.57-4.70 (m, 1H), 2.88-3.03 (m, 1H), 2.68 (s, 1H), 2.52 (s, 5H), 2.07-2.27 (m, 1H), 1.97 (br s, 1H), 1.72-1.91 (m, 2H), NH and OH not observed.

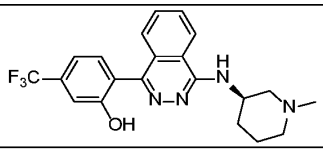
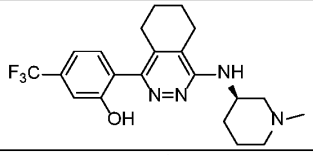
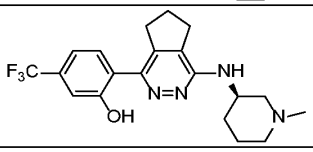
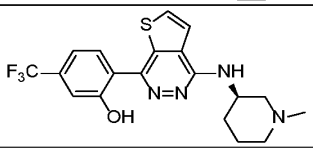
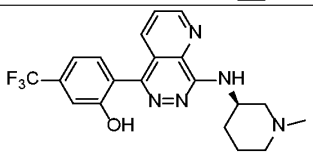
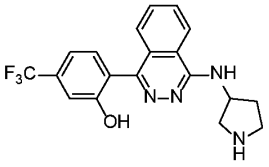
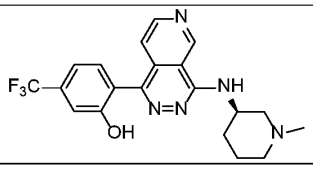
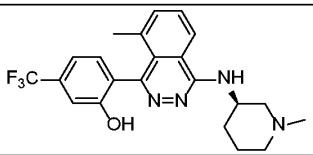
BIOLOGICAL ASSAYS

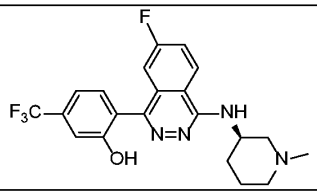
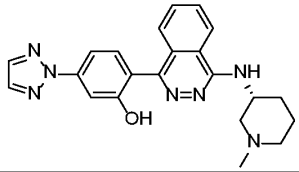
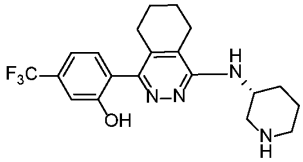
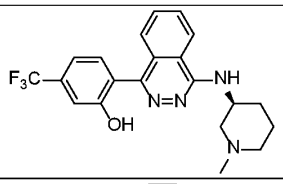
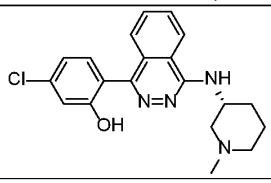
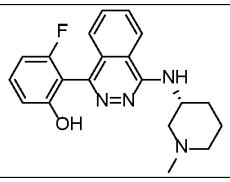
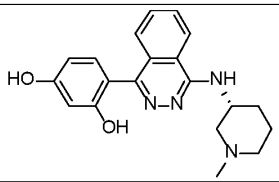
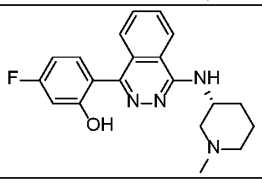
IL-1β Secretion Assay:

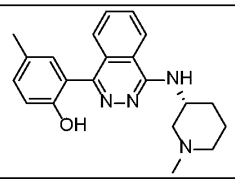
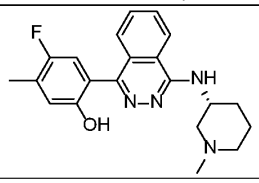
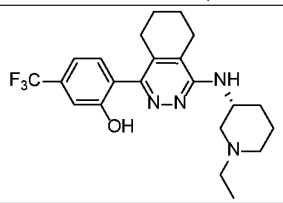
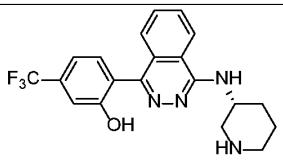
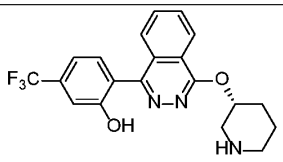
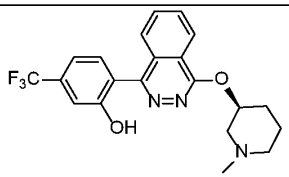
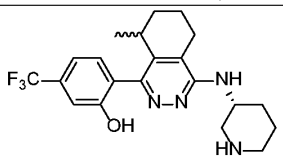
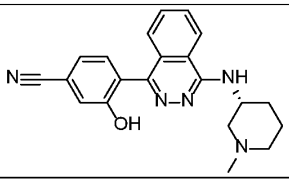
Monocytic THP-1 cells (ATCC: TIB-202) were maintained in growth media consisting of RPMI 1640 medium (ThermoFisher, Cat# 11875-085), 10% FBS (ThermoFisher) and 0.05mM β-mercaptoethanol (ThermoFisher, Cat# 21985-023), according to the provider's instructions. The cell concentration was adjusted to $7.5x10^5$cells/mL, and plated in complete growth media with a final concentration of 100ng/mL phorbol 12-myristate 13-acetate (PMA, Sigma #P8139). Cells were seeded at 100µL/well into a 96-well cell culture plate (ThermoFisher Cat#165305) and allowed to differentiate for 24 h in a cell culture incubator at 37°C with 5% CO_2. Cells were washed 1x with 100ul PBS and replaced with fresh RPMI + 5% FBS. Compounds were serial diluted in DMSO with 3 fold dilution for a total of 7 concentrations. Diluted compounds were added to the cells at a ratio of 1:200 and incubated for 20 h. The NLRP3 inflammasome was activated with the addition of 2.5µM Nigericin (Sigma: Cat# SML1779-1ml), for 3 h. After incubation, 15µL of conditioned media was removed and assayed for levels of IL-1β using the HTRF IL-1β assay kit (Cisbio: Cat# 62HIL1BPEH) as per the manufacturer's instructions.

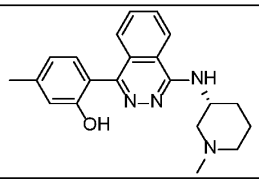
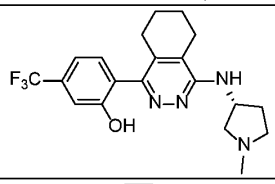
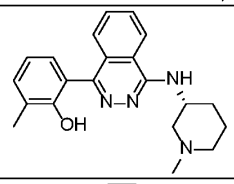
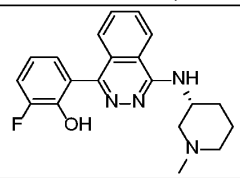
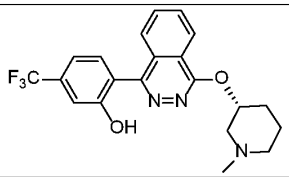
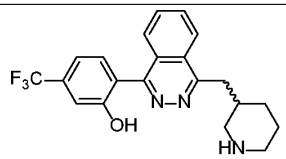
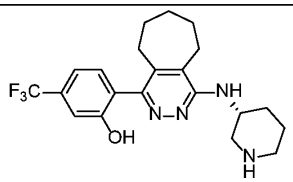
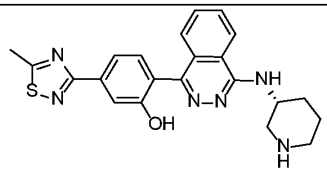
Compounds, once produced and prepared according to the present invention, can be assessed in variety of assays to characterize their activities. For example, NLRP3-dependent IL1β secretion was evaluated in THP1 cells. IC50 values of IL1β inhibition were calculated from the plot of percentage of inhibition versus the inhibitor concentration by a logistics fit. TABLE I depict examples of compounds according to generic Formulae I. Data which is < 1nM is listed as *****; data 1 - 10nM is listed as ****; data 10 - 100nM is listed as ***, data 100 - 300nM is listed as **, data ≥300 nM is listed as *. The data obtained from the THP1 NLRP3-dependent IL-1β secretion assay demonstrate that the compounds of the present invention could be used to treat diseases mediated through NLRP3 activation.

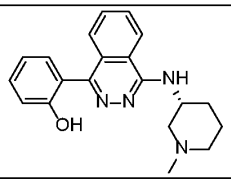
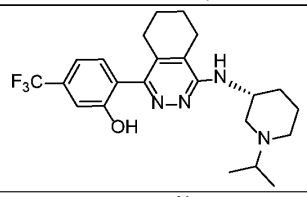
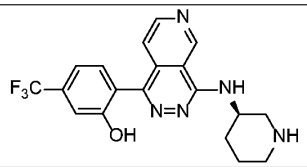
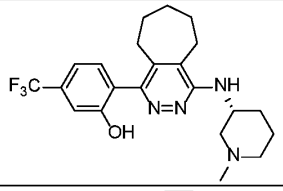
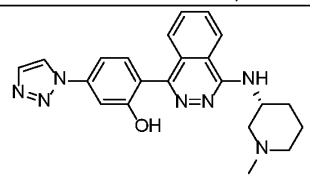
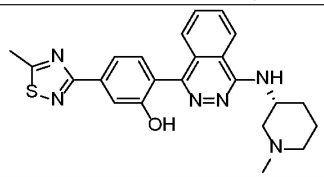
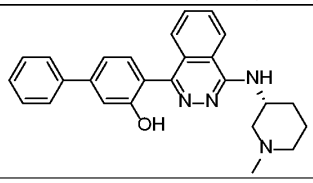
TABLE I.

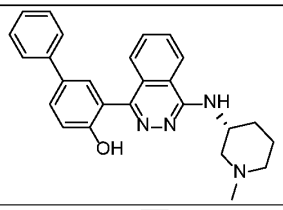
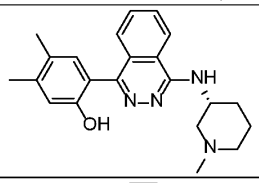
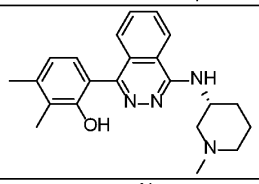
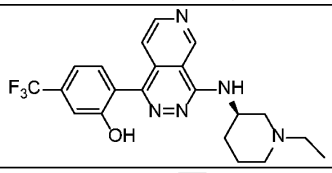
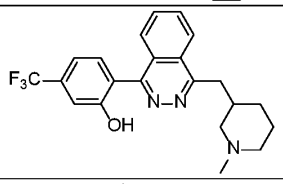
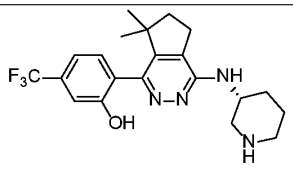
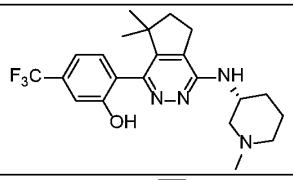
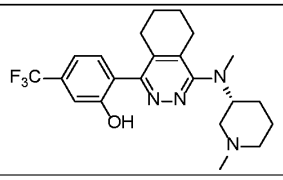
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-1		*****
I-2		*****
I-3		****
I-4		****
I-5		*****
I-6		***
I-7		*****
I-8		****

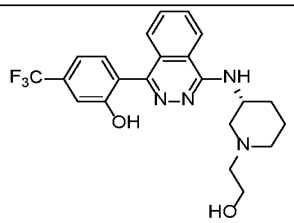
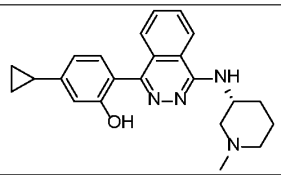
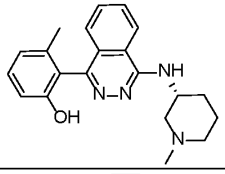
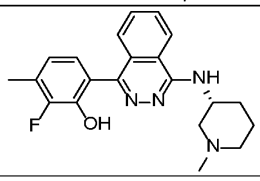
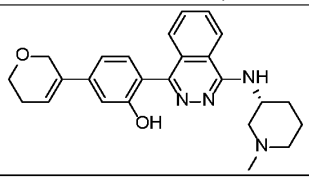
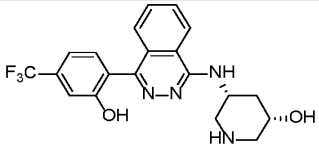
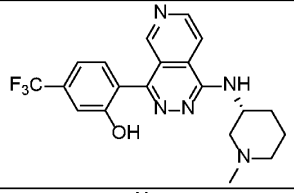
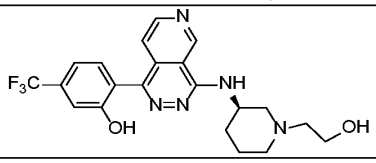
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-9		****
I-10		****
I-11		***
I-12		**
I-13		*****
I-14		****
I-15		**
I-16		****

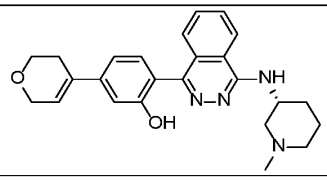
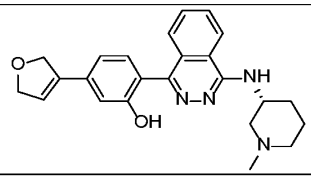
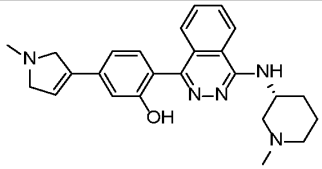
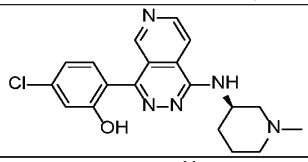
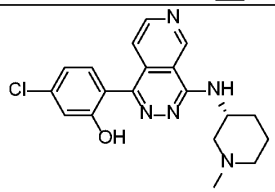
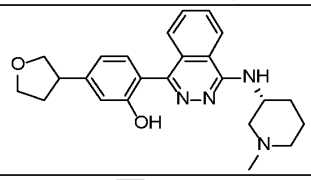
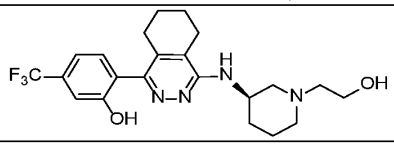
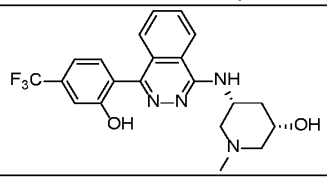
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-17		**
I-18		****
I-19		*****
I-20		*****
I-21		***
I-22		**
I-23		***
I-24		*****

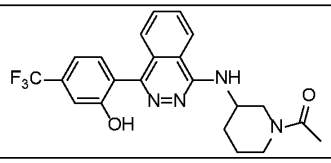
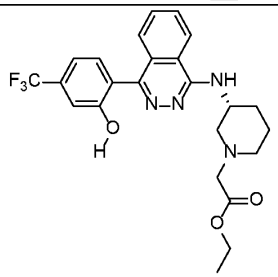
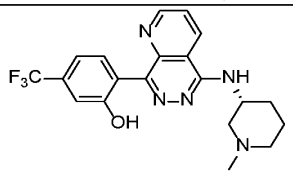
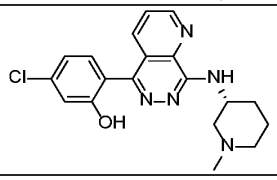
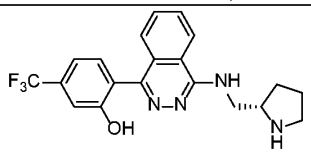
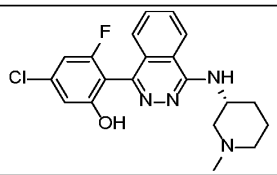
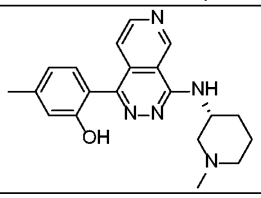
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-25		*****
I-26		***
I-27		*****
I-28		***
I-29		****
I-30		***
I-31		*****
I-32		***

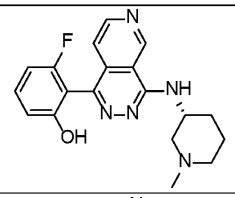
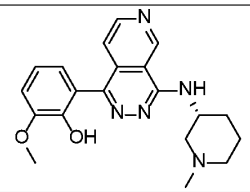
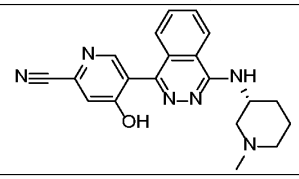
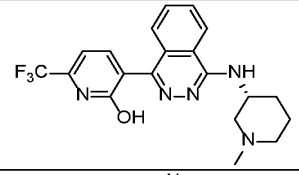
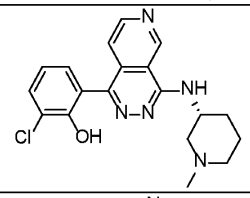
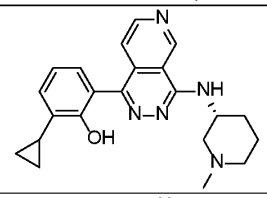
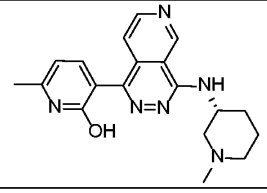
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-33		****
I-34		*****
I-35		*****
I-36		*****
I-37		***
I-38		*****
I-39		****

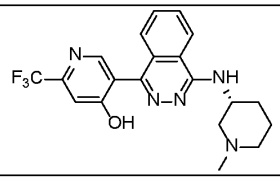
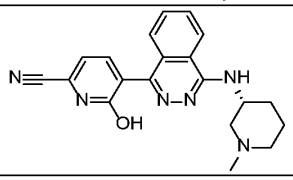
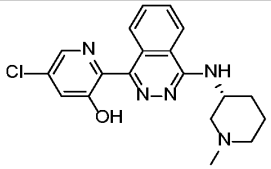
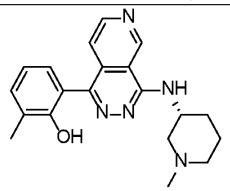
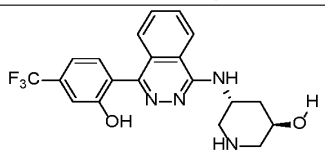
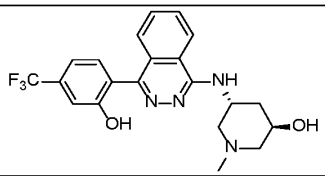
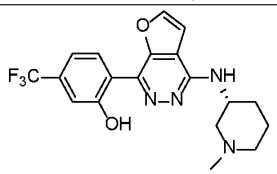
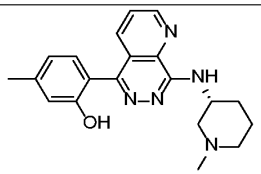
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-40		**
I-41		****
I-42		*****
I-43		*****
I-44		****
I-45		****
I-46		***
I-47		*****

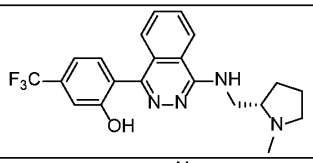
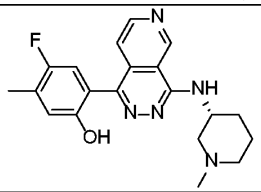
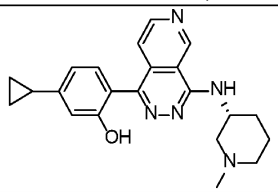
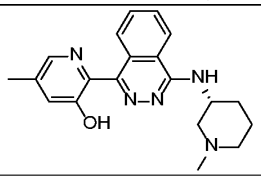
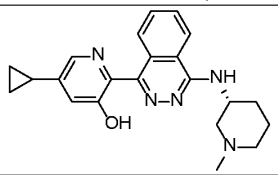
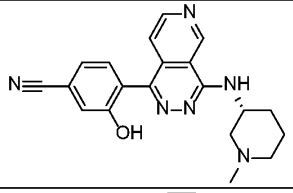
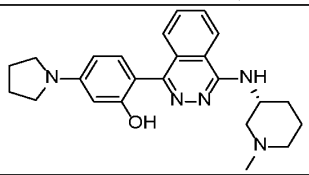
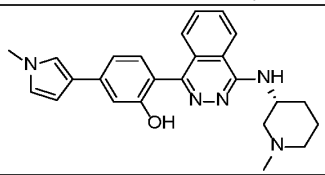
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-48		*****
I-49		*****
I-50		*****
I-51		*****
I-52		****
I-53		****
I-54		*****
I-55		*****

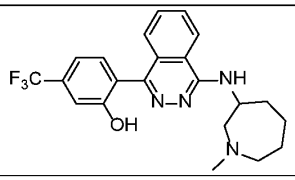
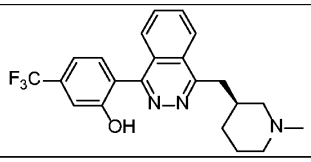
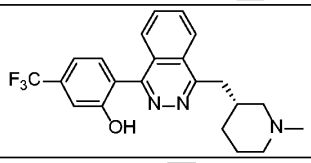
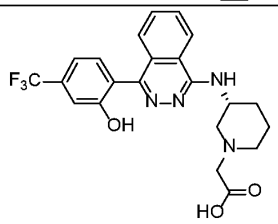
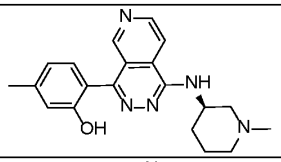
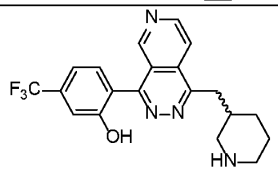
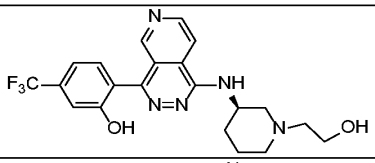
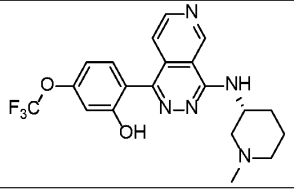
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-56		***
I-57		****
I-58		****
I-59		*****
I-60		*****
I-61		****
I-62		*****
I-63		****

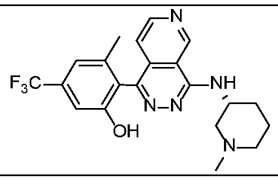
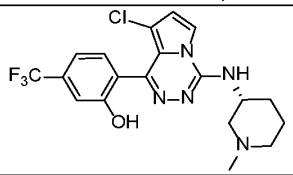
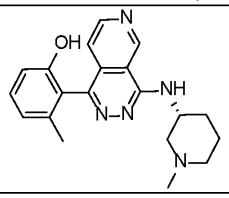
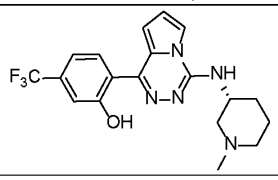
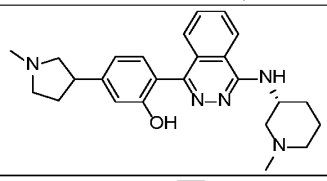
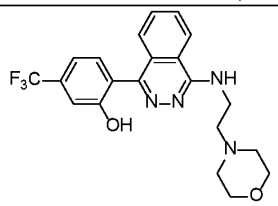
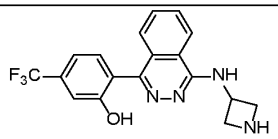
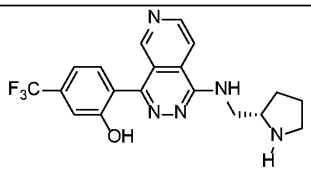
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-64		***
I-65		*****
I-66		****
I-67		*****
I-68		*****
I-70		*****
I-71		*****

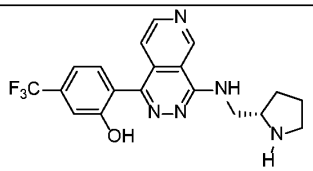
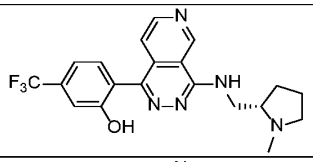
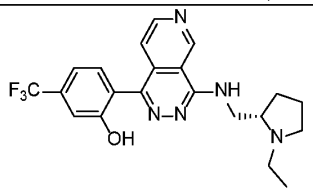
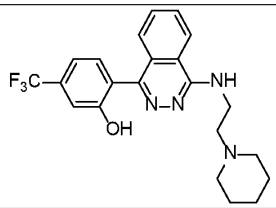
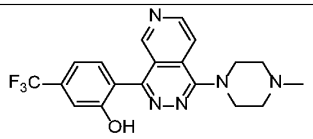
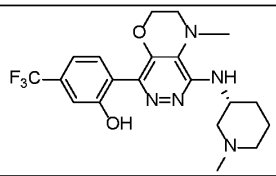
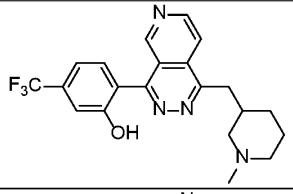
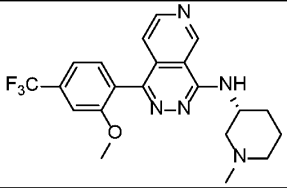
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-72		****
I-73		*****
I-74		***
I-75		***
I-76		*****
I-77		*****
I-78		***

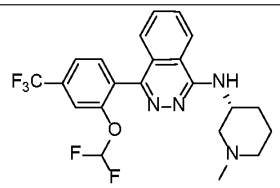
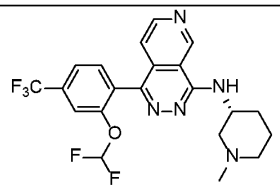
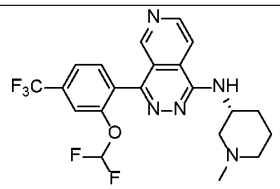
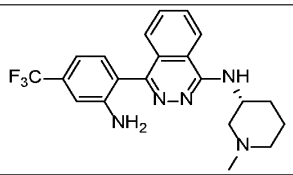
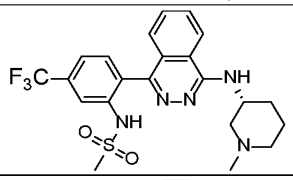
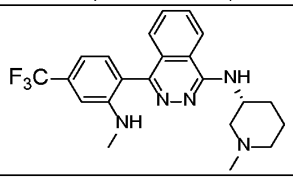
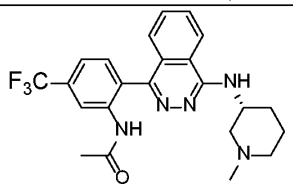
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-79		***
I-80		**
I-81		***
I-82		*****
I-83		***
I-84		***
I-85		***
I-86		*****

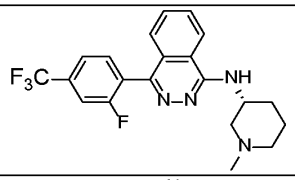
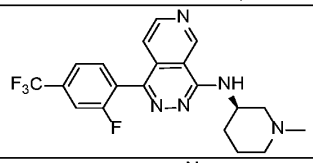
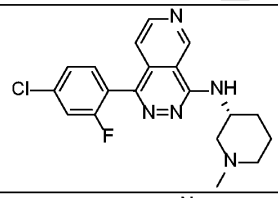
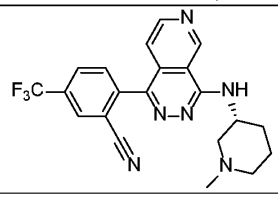
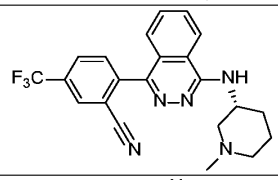
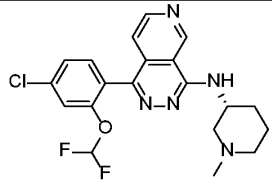
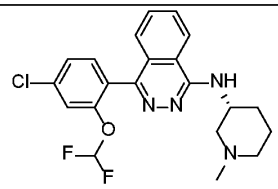
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-87		****
I-88		*****
I-89		*****
I-90		****
I-91		*****
I-92		*****
I-93		****
I-94		****

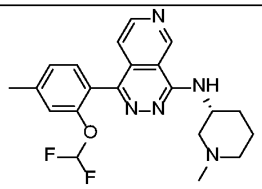
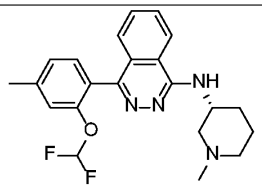
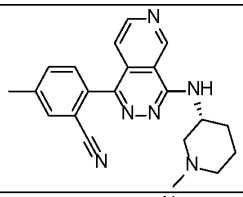
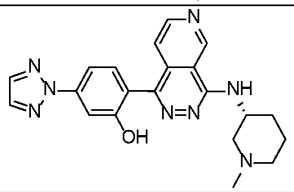
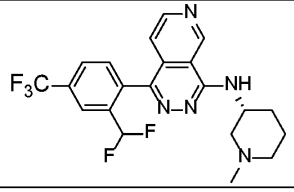
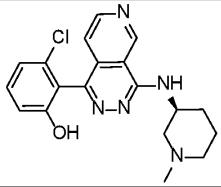
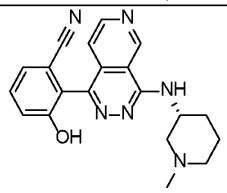
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-95		****
I-96		*
I-97		*****
I-98		*****
I-99		*****
I-100		****
I-101		*****
I-102		*****

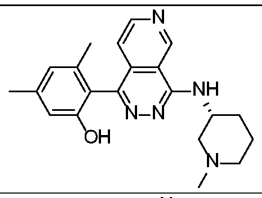
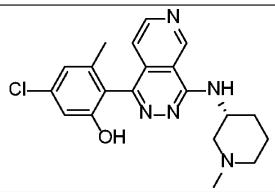
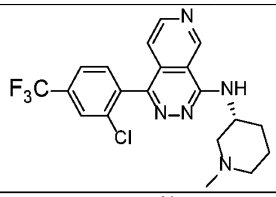
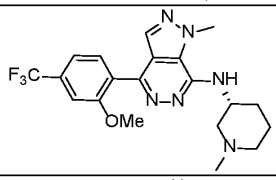
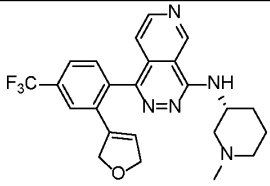
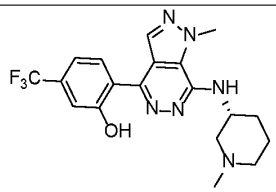
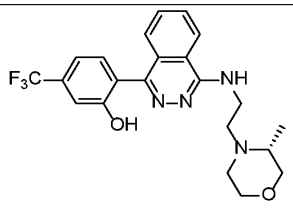
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-103		*****
I-104		****
I-105		****
I-106		*****
I-107		***
I-108		***
I-109		***
I-110		*****

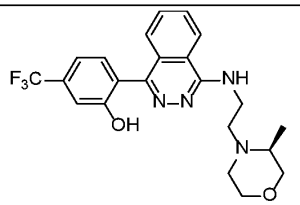
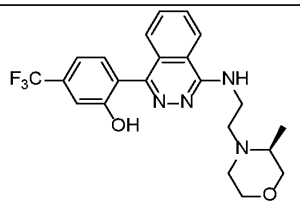
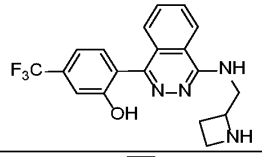
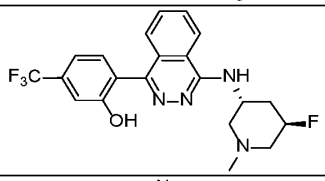
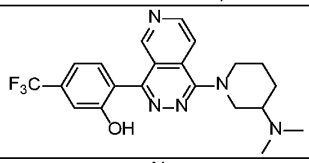
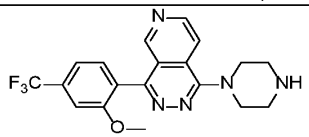
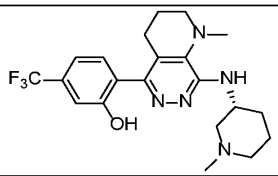
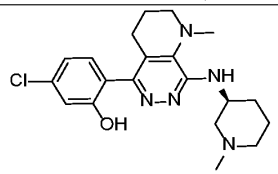
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-111		****
I-112		*****
I-113		*****
I-115		**
I-116		**
I-117		***
I-118		****
I-119		****

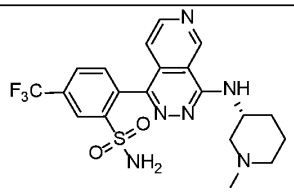
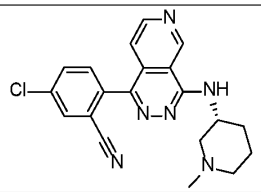
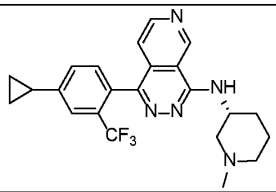
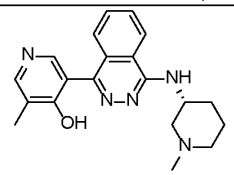
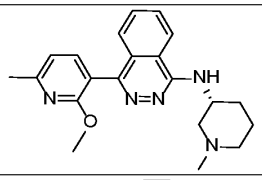
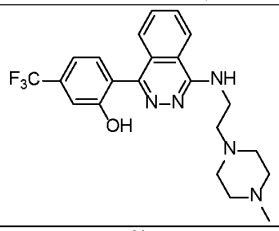
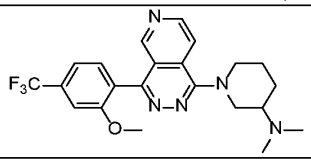
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-120		****
I-121		*****
I-122		****
I-123		****
I-124		****
I-125		****
I-126		****

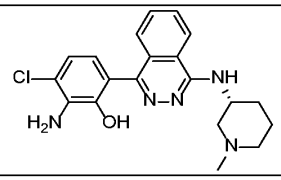
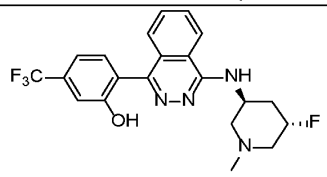
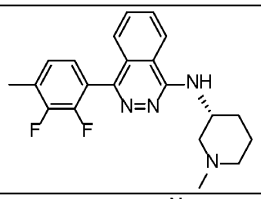
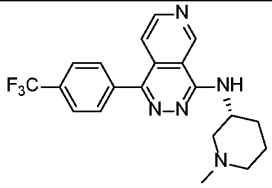
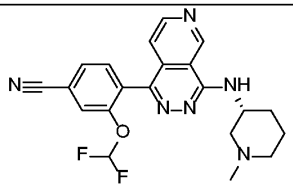
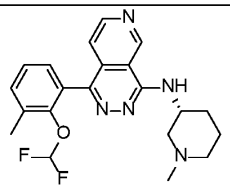
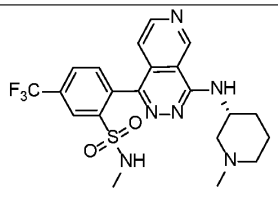
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-127		****
I-128		****
I-129		*****
I-130		****
I-131		****
I-132		*****
I-133		****

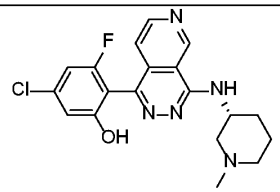
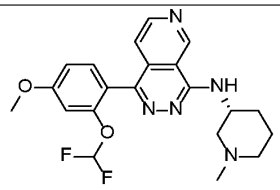
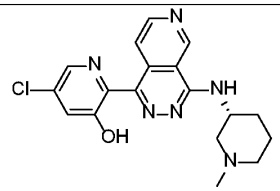
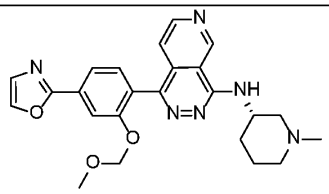
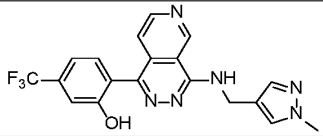
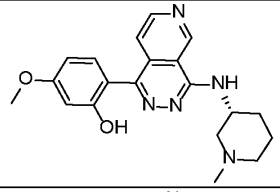
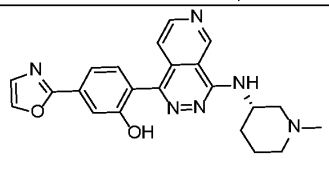
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-134		****
I-135		****
I-136		****
I-137		*****
I-138		****
I-139		****
I-140		****

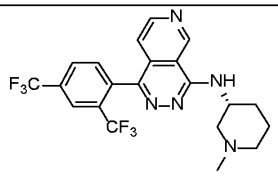
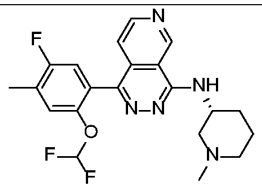
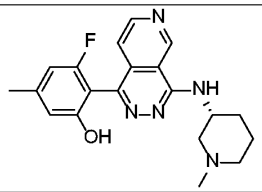
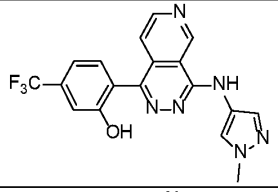
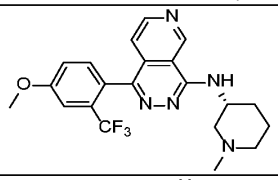
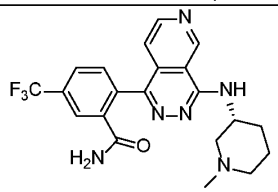
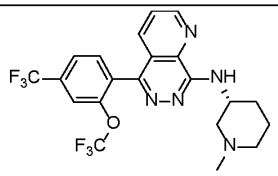
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-141		****
I-142		*****
I-143		****
I-144		****
I-145		****
I-146		*****
I-147		***

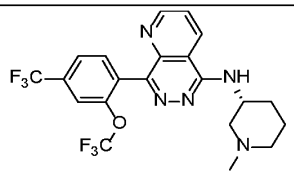
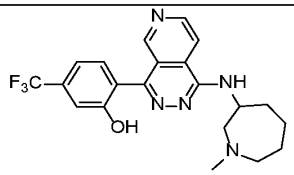
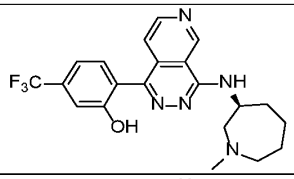
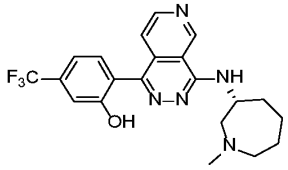
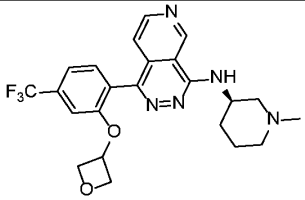
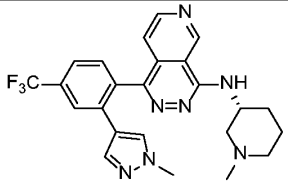
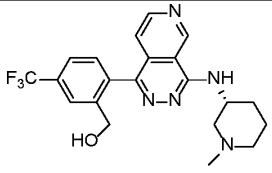
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-148		***
I-149		***
I-150		***
I-151		*****
I-152		****
I-153		***
I-154		****
I-155		****

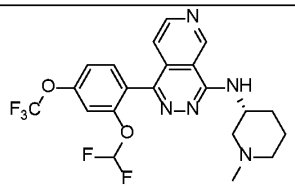
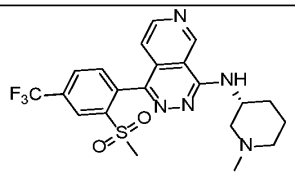
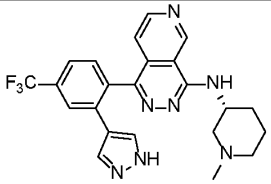
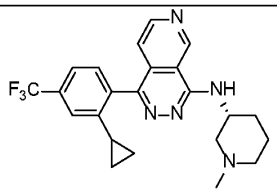
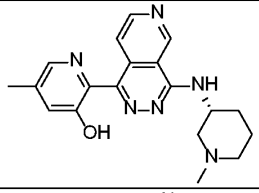
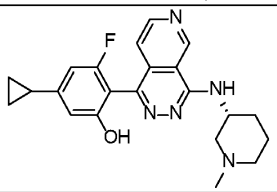
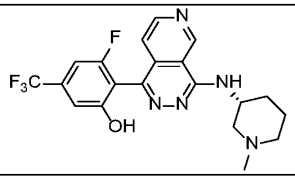
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-156		**
I-157		****
I-158		*****
I-159		**
I-160		**
I-161		***
I-162		***

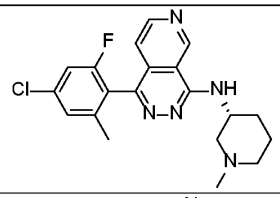
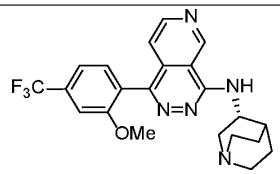
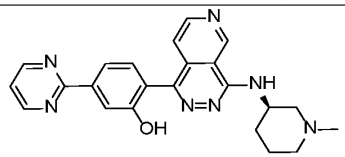
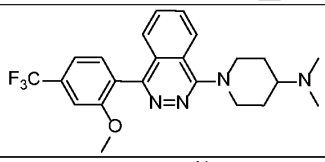
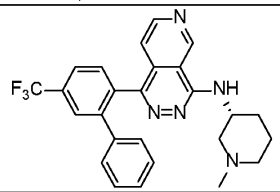
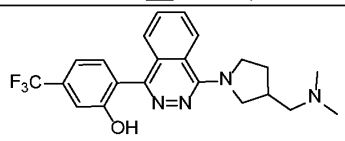
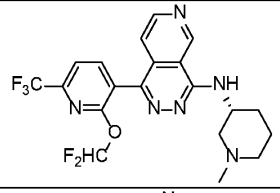
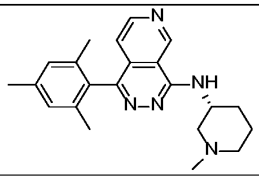
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-163		***
I-164		***
I-165		***
I-166		****
I-167		***
I-168		***
I-169		***

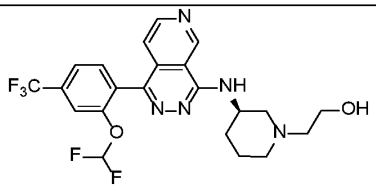
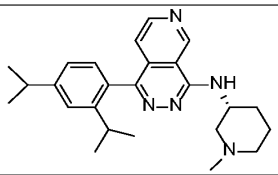
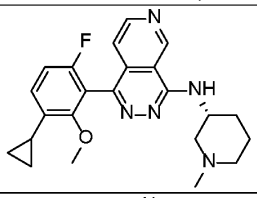
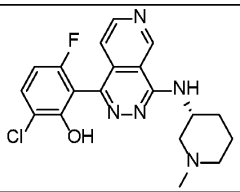
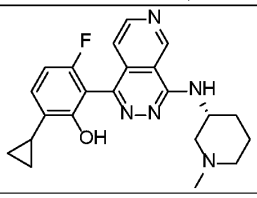
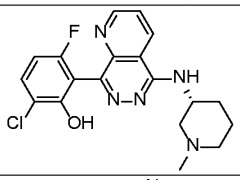
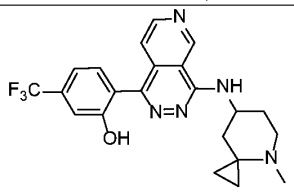
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-170		*****
I-171		*****
I-172		****
I-173		***
I-174		***
I-175		*****
I-176		****

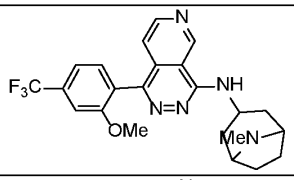
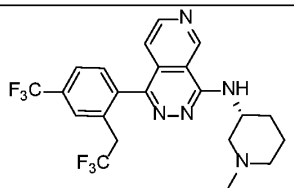
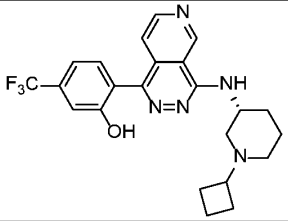
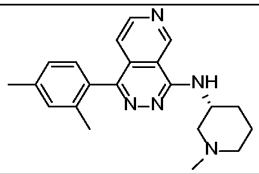
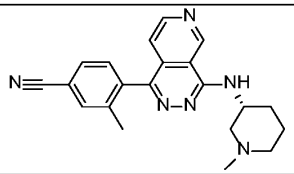
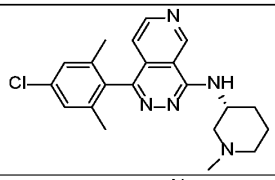
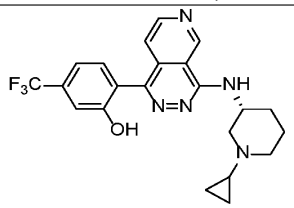
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-177		****
I-178		****
I-179		*****
I-180		****
I-181		****
I-182		***
I-183		****

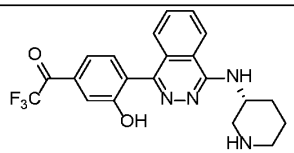
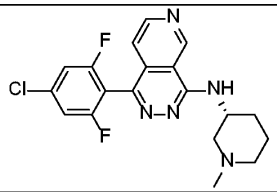
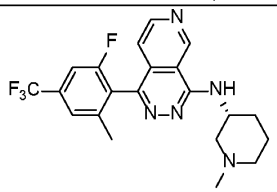
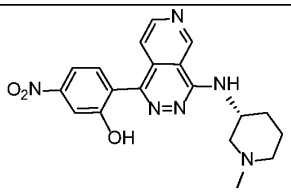
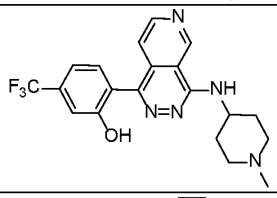
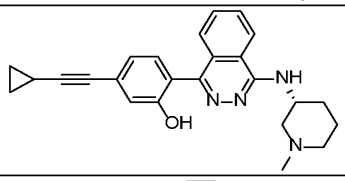
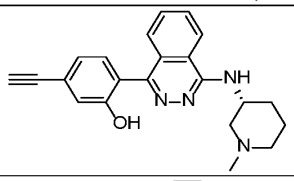
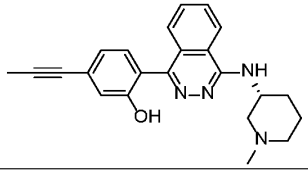
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-184		***
I-185		***
I-186		***
I-187		*****
I-188		***
I-189		***
I-190		***

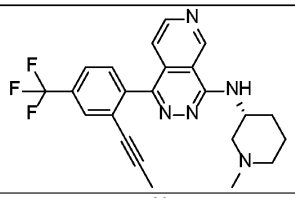
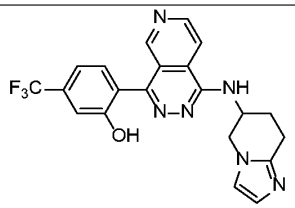
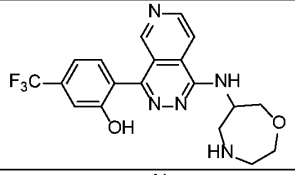
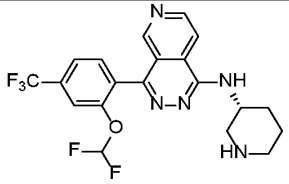
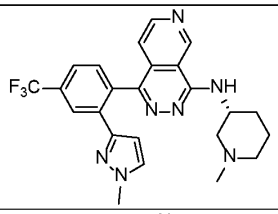
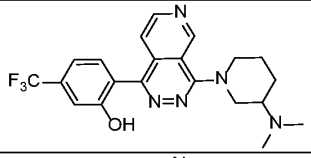
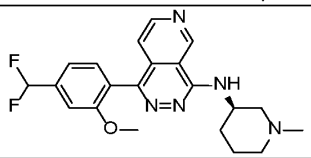
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-191		****
I-192		***
I-193		***
I-194		****
I-195		****
I-196		*****
I-197		*****

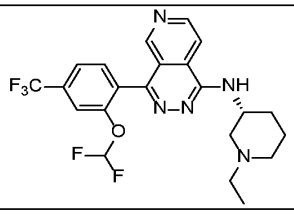
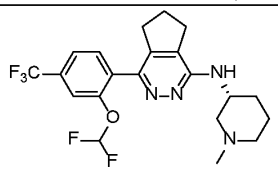
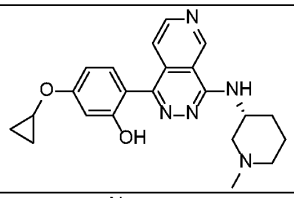
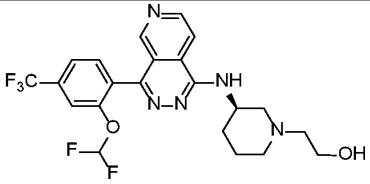
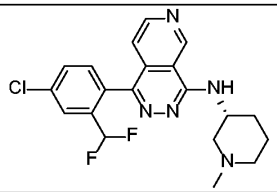
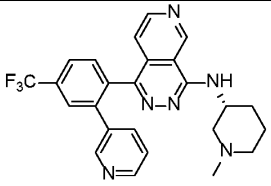
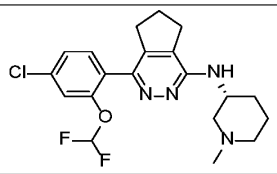
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-198		***
I-199		***
I-200		****
I-201		***
I-202		***
I-203		***
I-204		****
I-205		****

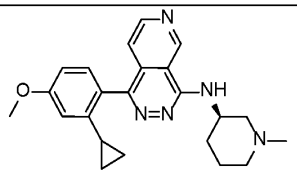
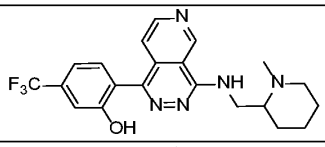
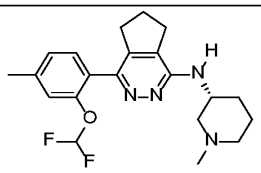
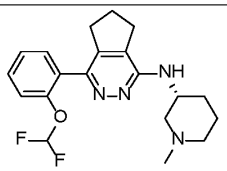
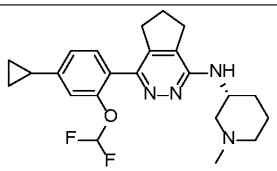
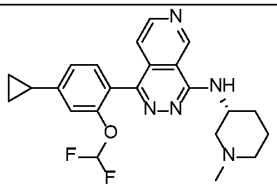
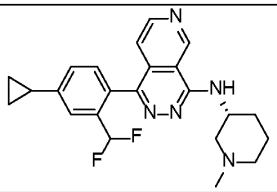
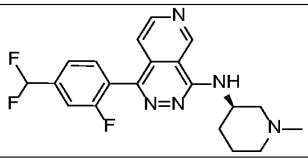
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-206		*****
I-207		****
I-208		***
I-209		****
I-210		***
I-211		***
I-212		***

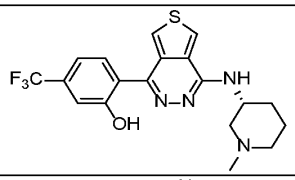
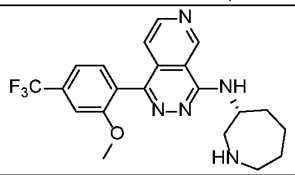
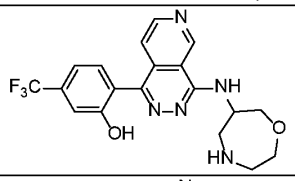
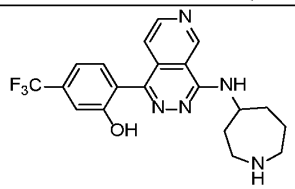
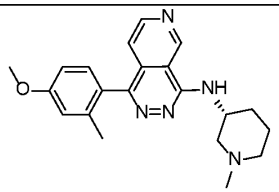
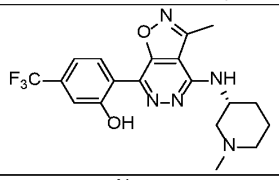
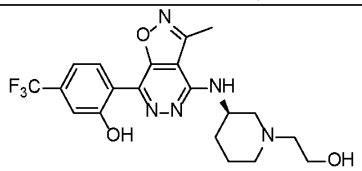
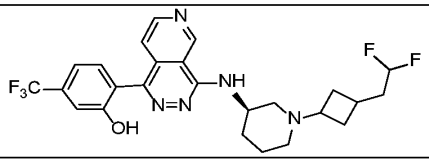
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-213		**
I-214		*****
I-215		*****
I-216		****
I-217		***
I-218		*****
I-219		*****

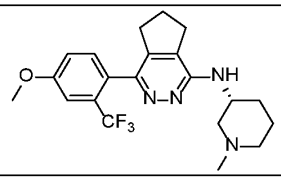
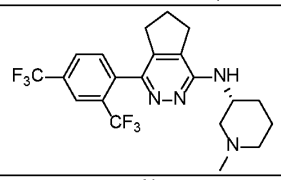
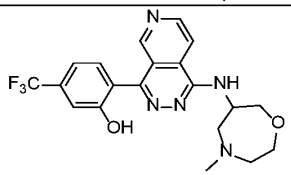
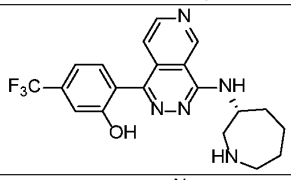
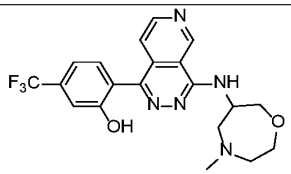
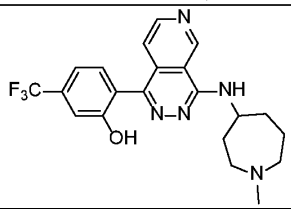
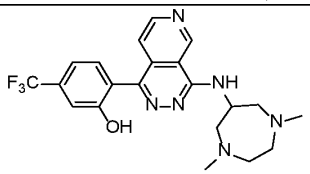
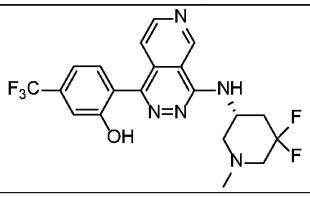
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-220		**
I-221		****
I-222		****
I-223		****
I-224		***
I-225		****
I-226		*****
I-227		*****

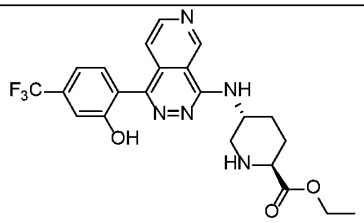
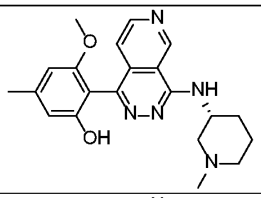
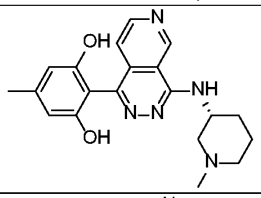
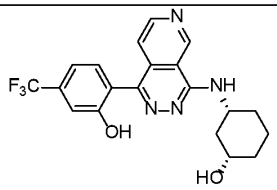
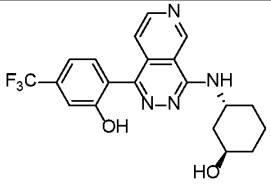
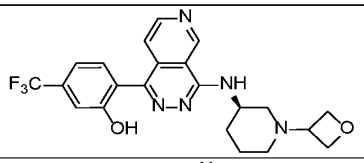
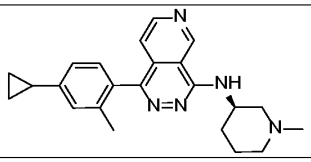
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-228		****
I-229		***
I-230		***
I-231		***
I-232		***
I-233		***
I-234		***

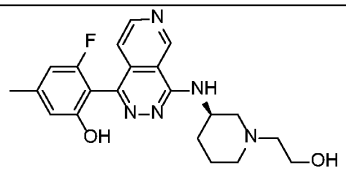
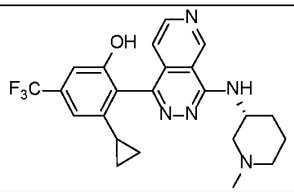
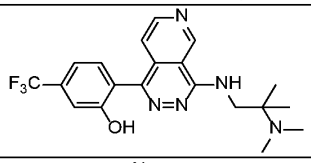
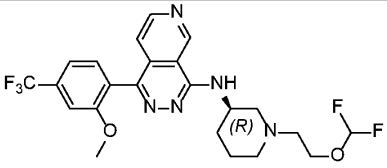
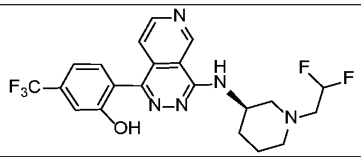
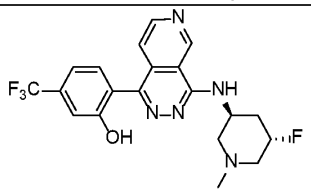
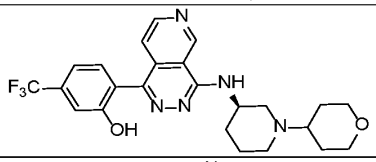
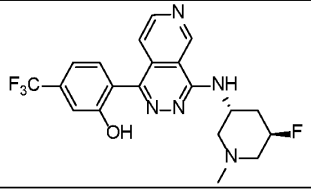
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-235		****
I-236		****
I-237		****
I-238		***
I-239		****
I-240		**
I-241		***

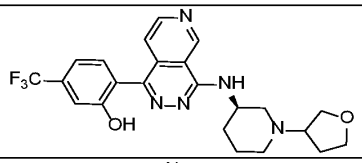
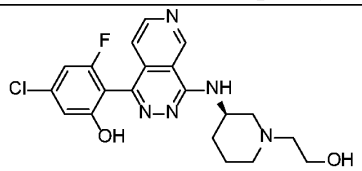
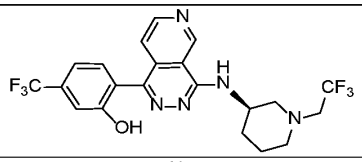
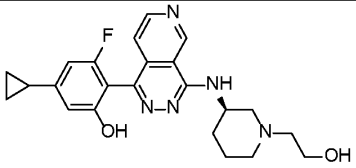
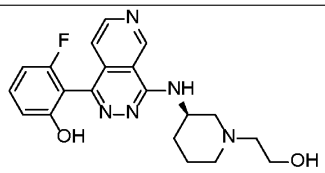
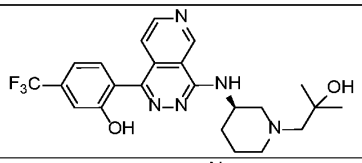
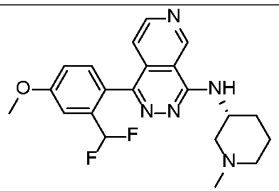
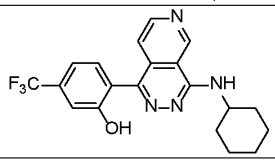
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-242		****
I-243		****
I-244		***
I-245		****
I-246		***
I-247		****
I-248		****
I-249		***

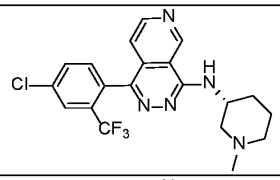
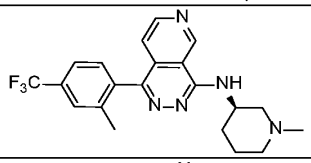
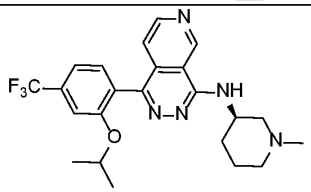
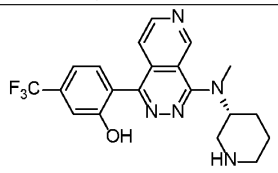
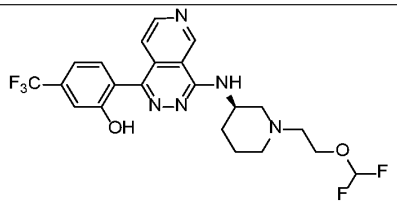
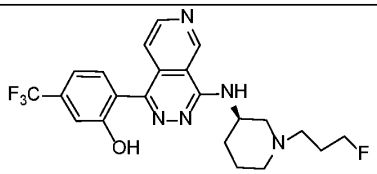
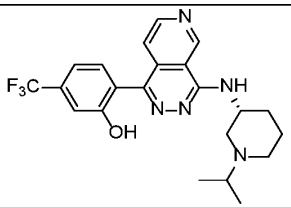
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-250		*****
I-251		**
I-252		***
I-253		****
I-254		****
I-255		****
I-256		***
I-257		****

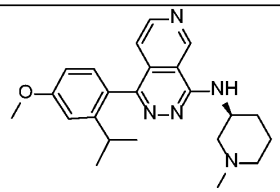
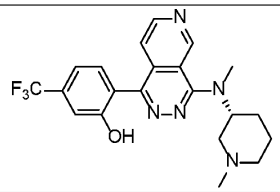
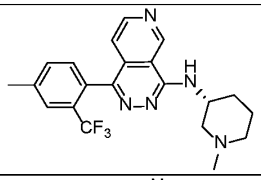
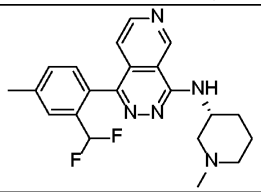
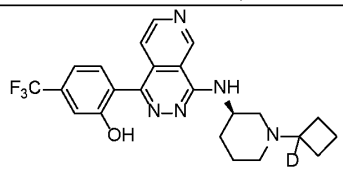
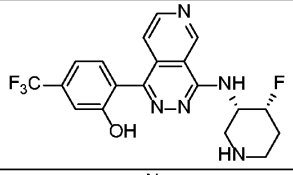
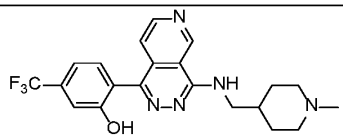
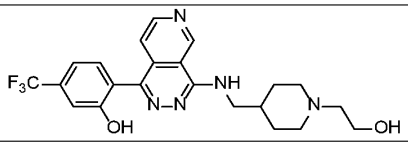
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-258		***
I-259		***
I-260		***
I-261		****
I-262		****
I-263		****
I-264		***
I-265		****

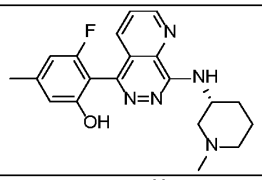
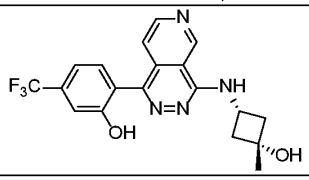
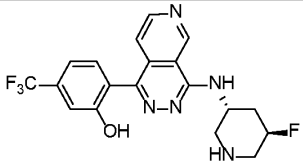
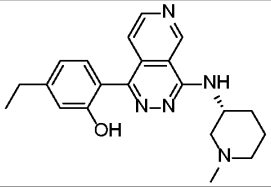
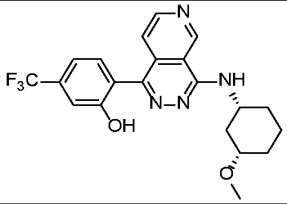
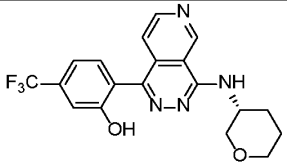
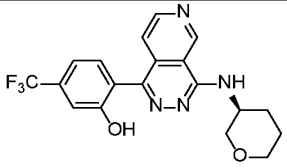
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-266		*****
I-267		****
I-268		*****
I-269		****
I-270		****
I-271		****
I-272		****

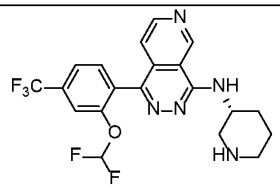
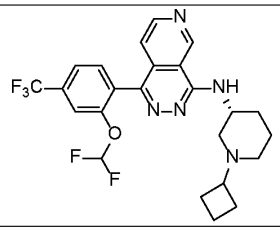
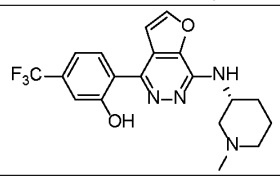
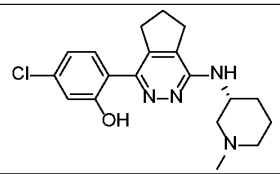
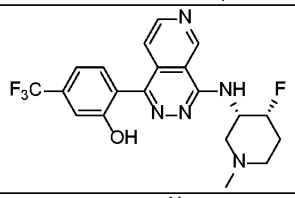
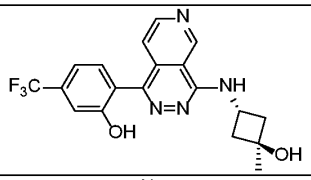
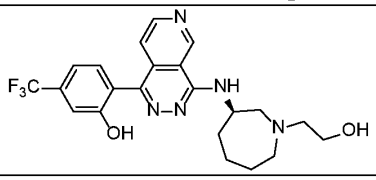
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-273		*****
I-274		****
I-275		****
I-276		***
I-277		*****
I-278		***
I-279		*****
I-280		*****

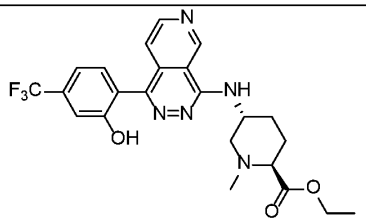
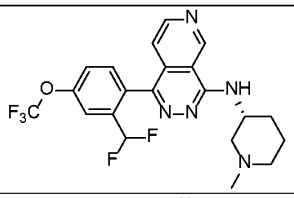
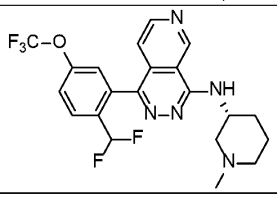
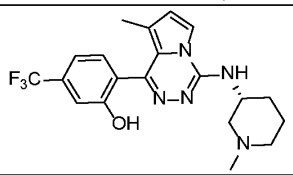
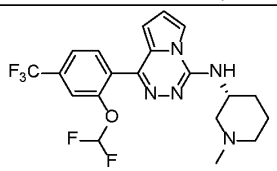
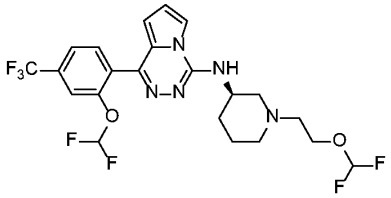
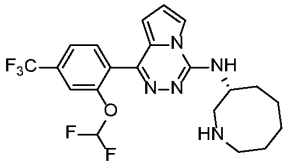
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-281		*****
I-282		*****
I-283		*****
I-284		*****
I-285		****
I-286		*****
I-287		****
I-288		****

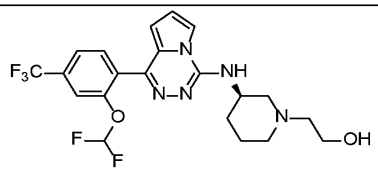
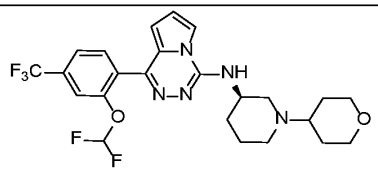
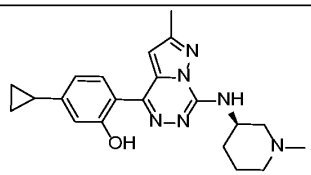
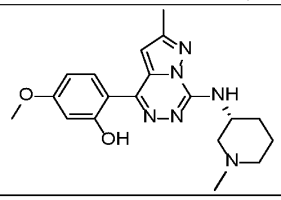
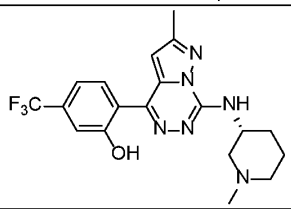
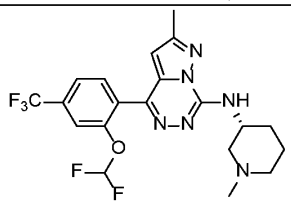
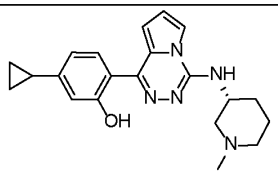
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-289		****
I-290		****
I-291		****
I-292		****
I-293		*****
I-294		*****
I-295		*****

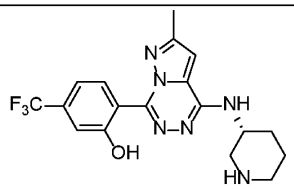
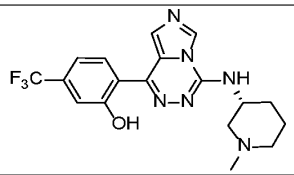
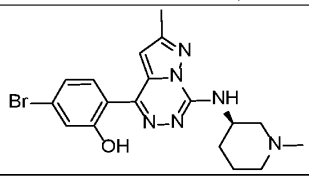
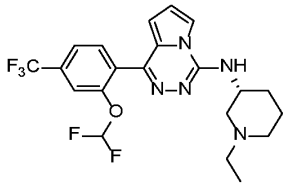
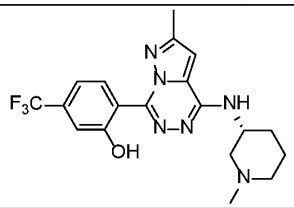
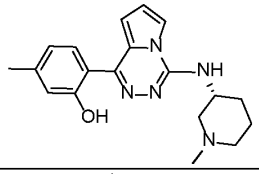
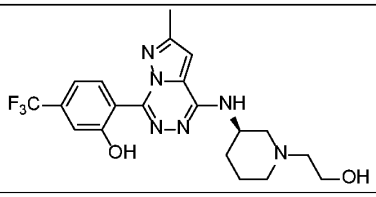
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-296		****
I-297		*****
I-298		****
I-299		*****
I-300		*****
I-301		****
I-302		****
I-303		****

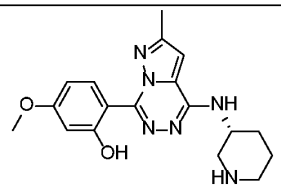
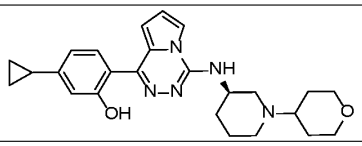
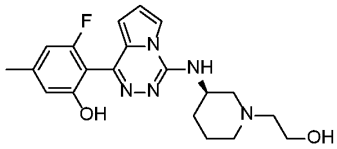
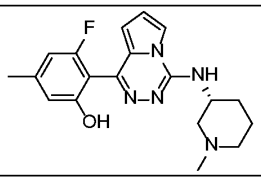
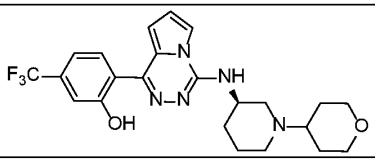
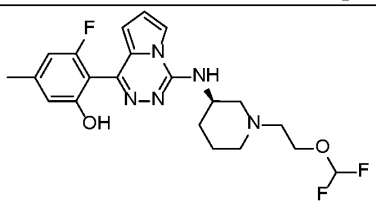
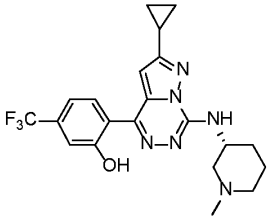
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-304		*****
I-305		*****
I-306		*****
I-307		*****
I-308		*****
I-309		****
I-310		****

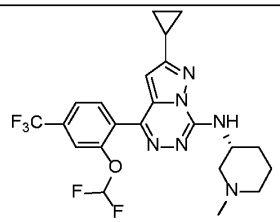
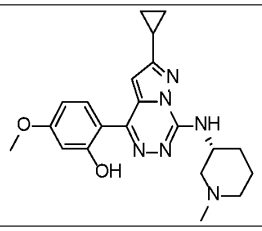
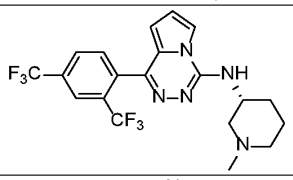
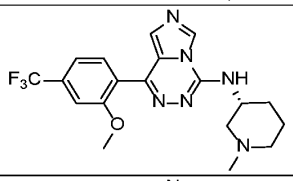
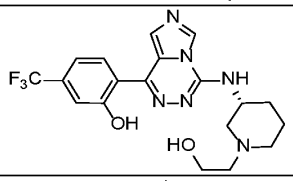
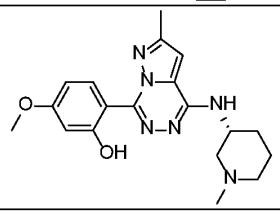
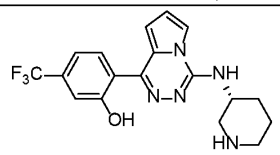
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-311		****
I-312		*****
I-313		*****
I-314		****
I-315		*****
I-316		****
I-317		****

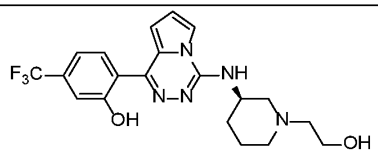
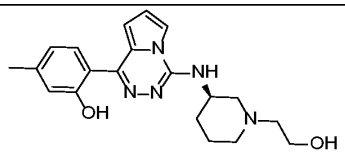
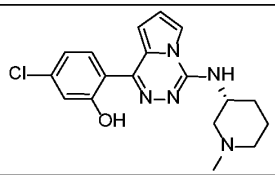
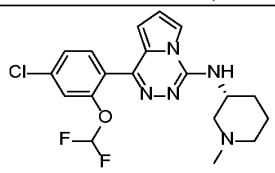
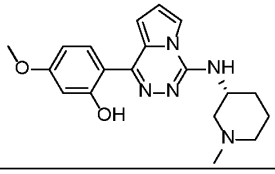
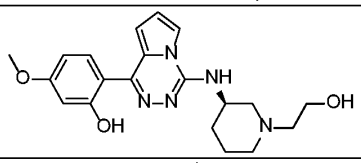
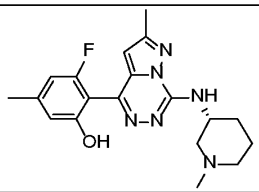
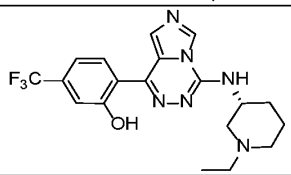
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-318		*****
I-319		****
I-320		****
I-321		***
I-322		*****
I-323		****
I-324		****

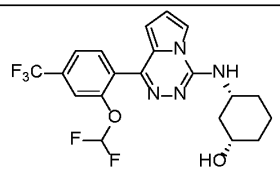
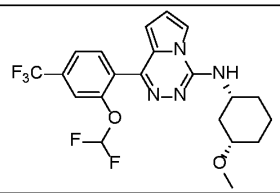
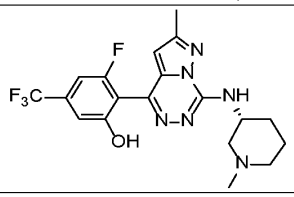
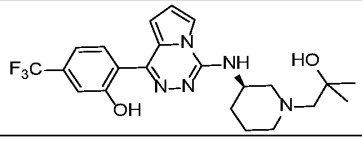
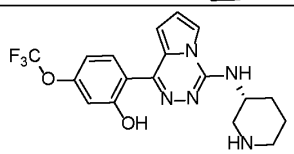
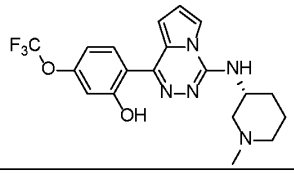
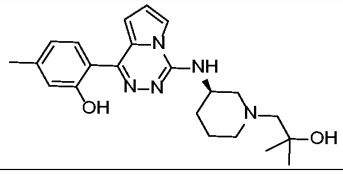
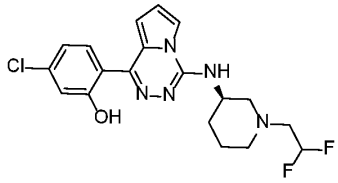
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-325		****
I-326		*****
I-327		****
I-328		*****
I-329		*****
I-330		****
I-331		****

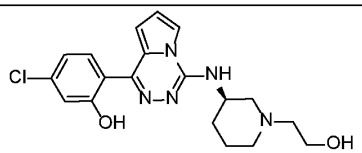
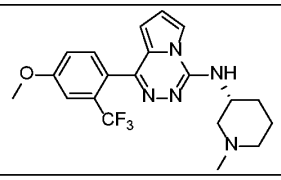
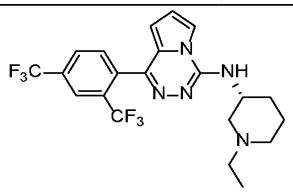
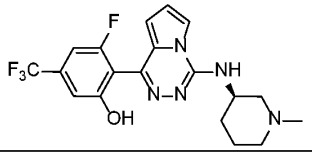
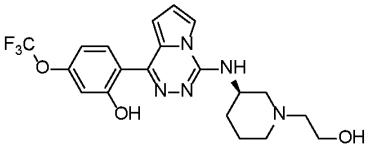
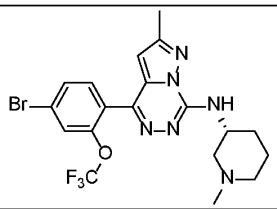
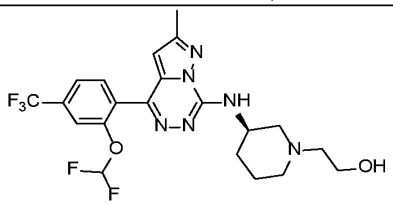
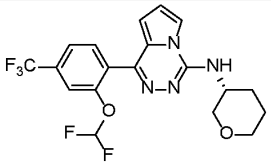
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-332		***
I-333		*****
I-334		*****
I-335		*****
I-336		***
I-337		****
I-338		***

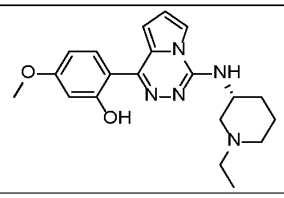
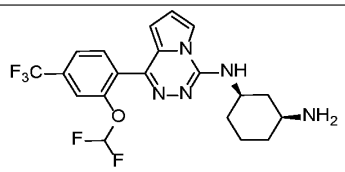
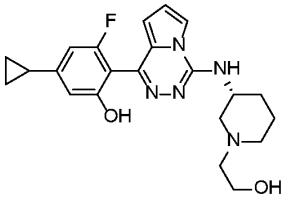
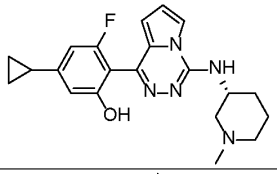
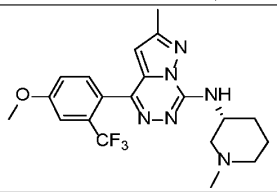
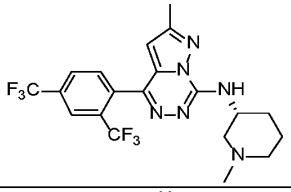
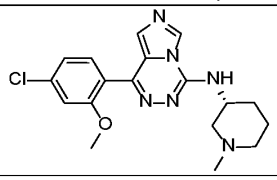
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-339		**
I-340		****
I-341		****
I-342		****
I-343		****
I-344		*****
I-345		****

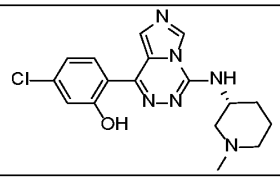
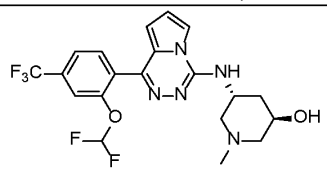
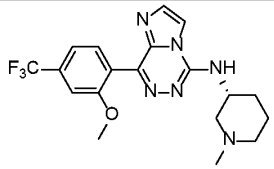
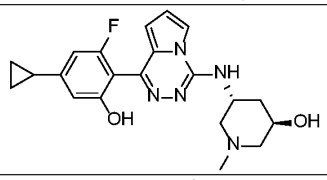
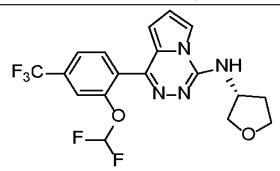
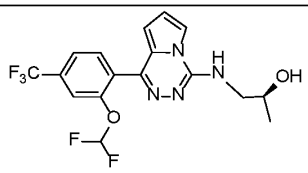
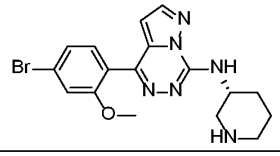
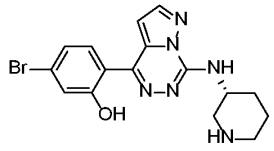
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-346		****
I-347		***
I-348		****
I-349		****
I-350		****
I-351		***
I-352		****

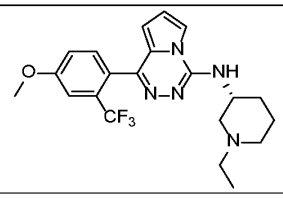
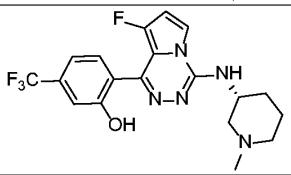
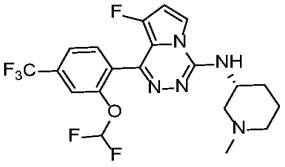
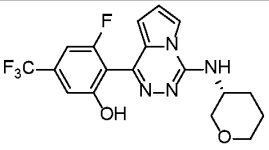
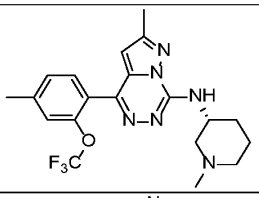
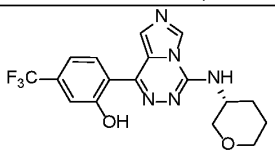
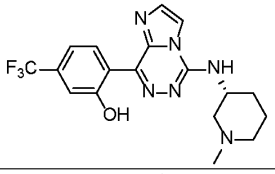
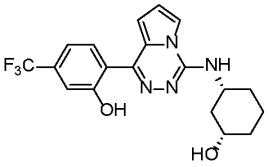
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-353		****
I-354		*****
I-355		*****
I-356		****
I-357		****
I-358		****
I-359		*****
I-360		*****

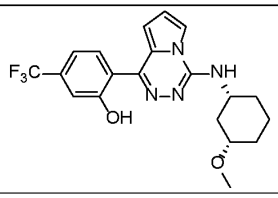
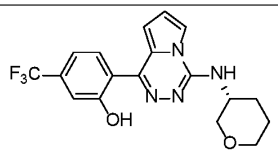
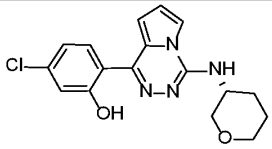
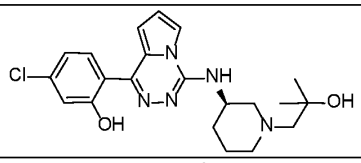
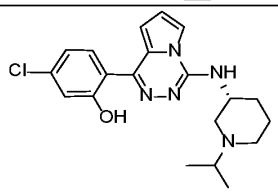
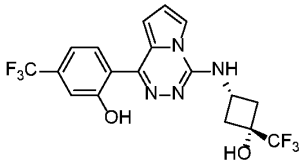
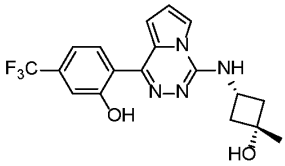
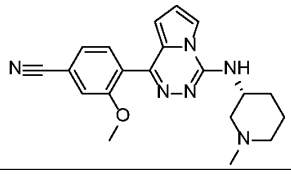
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-361		****
I-362		***
I-363		*****
I-364		****
I-365		***
I-366		****
I-367		***
I-368		***

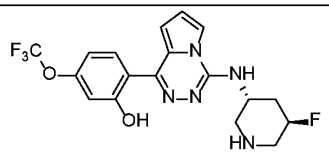
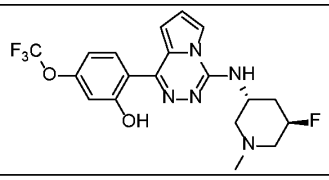
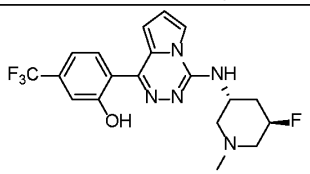
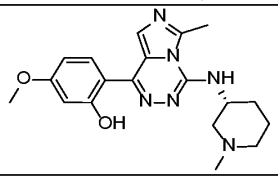
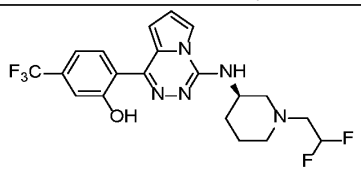
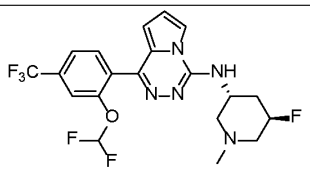
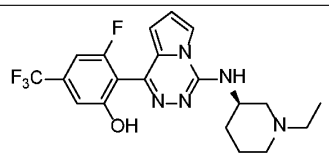
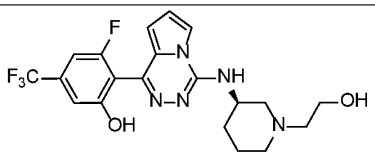
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-369		****
I-370		****
I-371		*****
I-372		*****
I-373		****
I-374		****
I-375		****
I-376		****

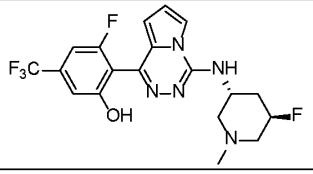
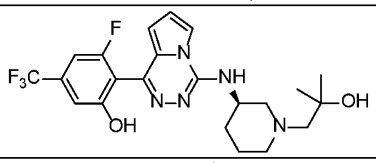
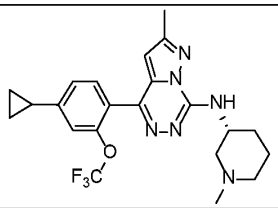
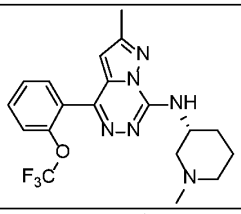
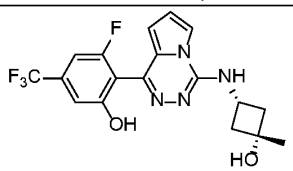
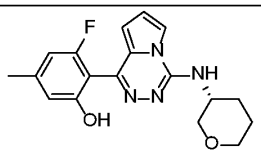
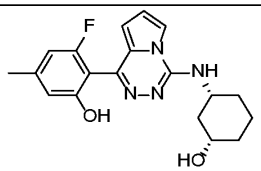
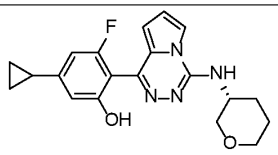
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-377		****
I-378		***
I-379		****
I-380		*****
I-381		****
I-382		****
I-383		****

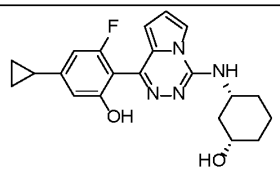
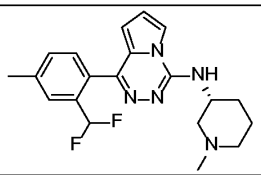
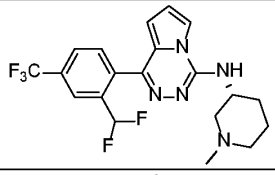
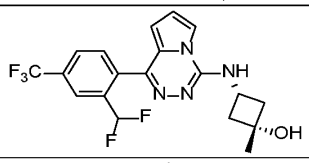
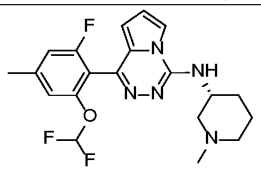
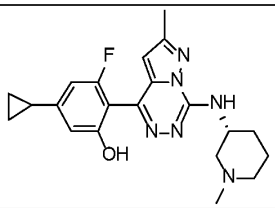
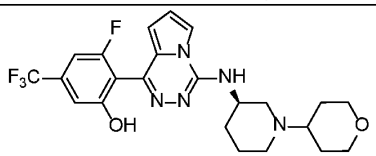
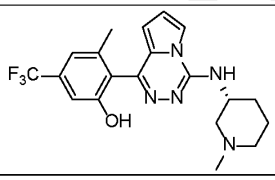
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-384		*****
I-385		**
I-386		**
I-387		***
I-388		****
I-389		****
I-390		**
I-391		****

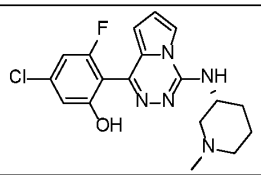
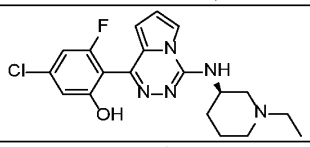
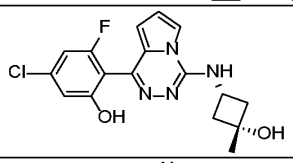
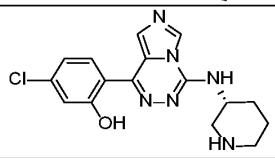
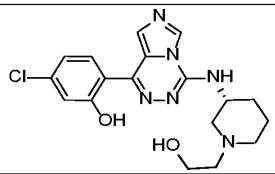
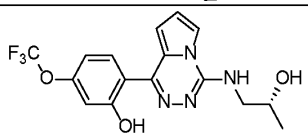
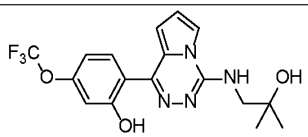
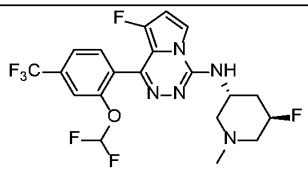
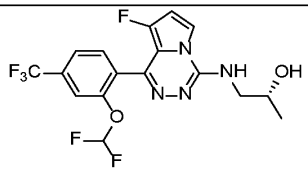
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-392		****
I-393		*****
I-394		****
I-395		***
I-396		***
I-397		***
I-398		*
I-399		***

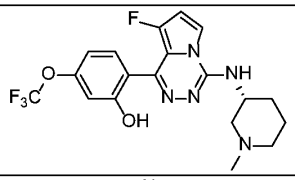
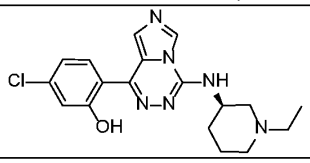
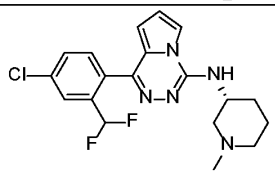
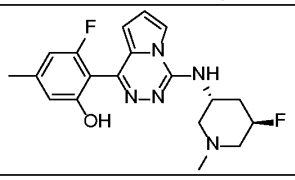
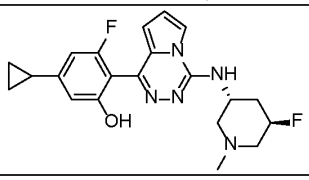
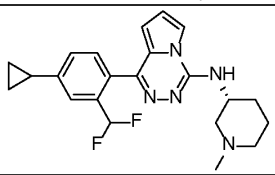
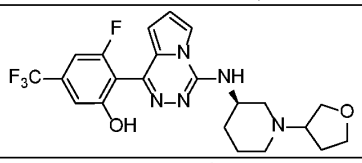
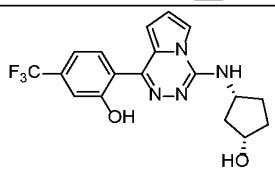
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-400		**
I-401		**
I-402		***
I-403		***
I-404		*****
I-405		**
I-406		****
I-407		***

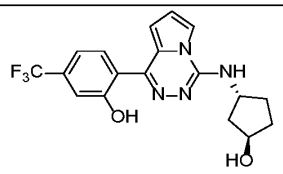
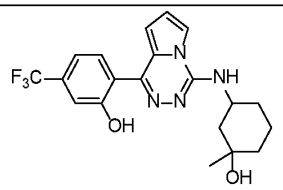
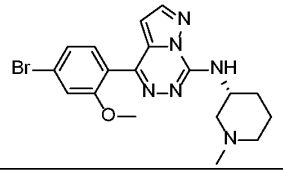
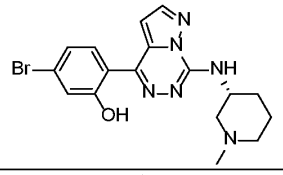
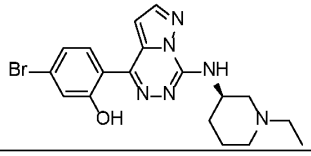
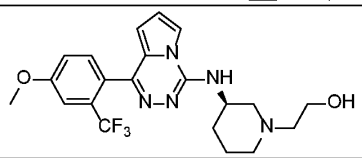
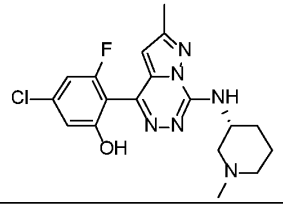
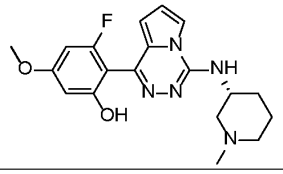
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-408		***
I-409		****
I-410		****
I-411		***
I-412		*****
I-413		****
I-414		*****
I-415		****

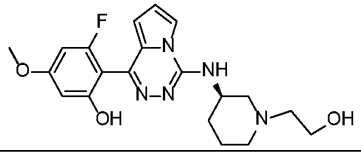
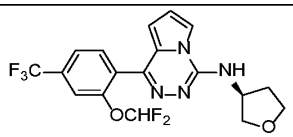
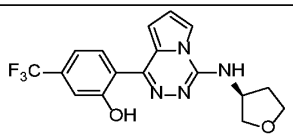
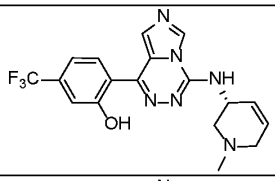
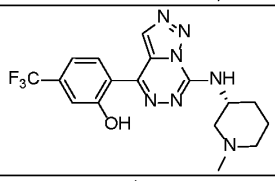
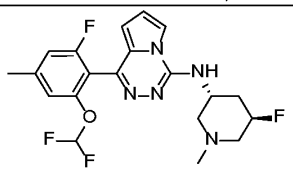
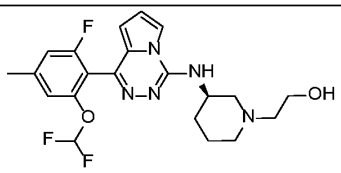
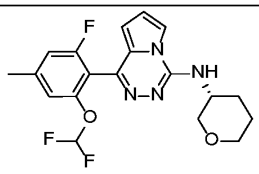
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-416		****
I-417		****
I-418		****
I-419		***
I-420		****
I-421		****
I-422		****
I-423		***

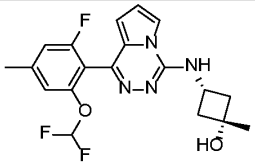
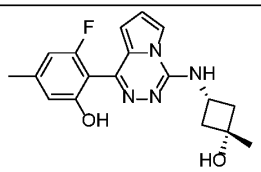
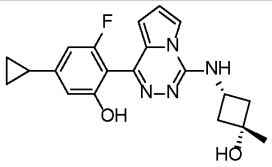
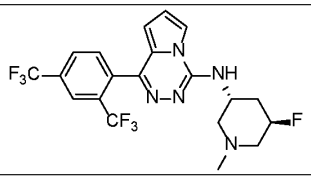
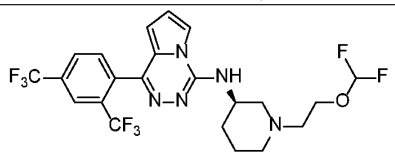
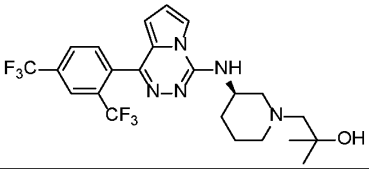
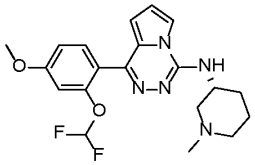
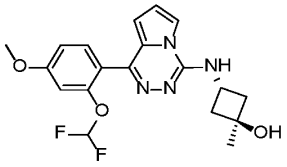
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-424		****
I-425		***
I-426		***
I-427		***
I-428		***
I-429		*****
I-430		****
I-431		*****

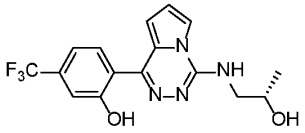
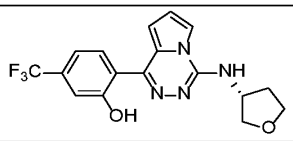
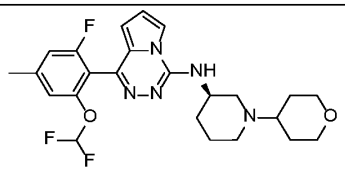
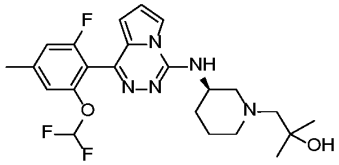
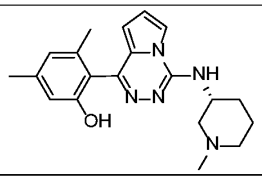
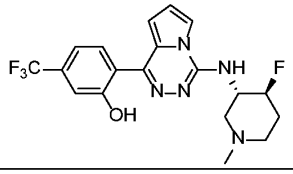
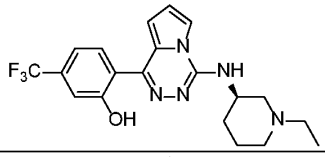
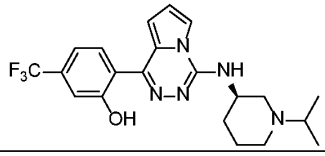
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-432		*****
I-433		*****
I-434		****
I-435		****
I-436		****
I-437		***
I-438		**
I-439		****
I-440		***

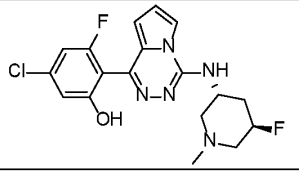
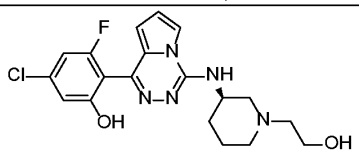
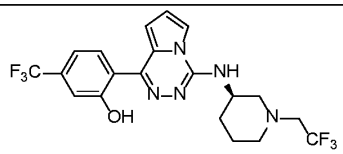
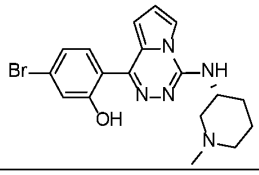
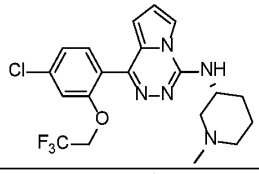
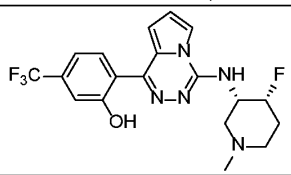
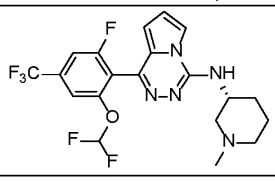
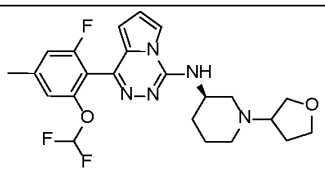
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-441		****
I-442		*****
I-443		****
I-444		*****
I-445		****
I-446		****
I-447		****
I-448		***

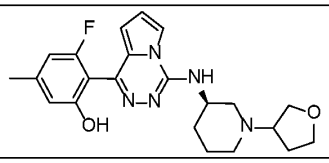
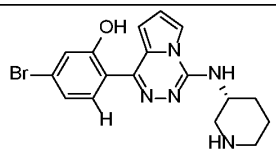
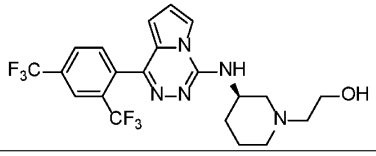
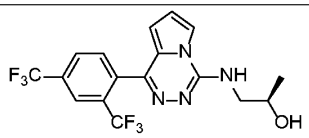
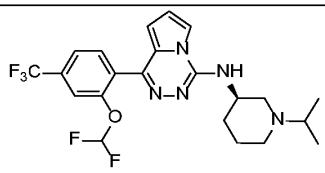
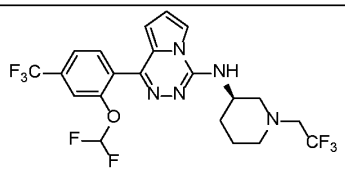
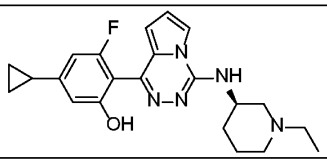
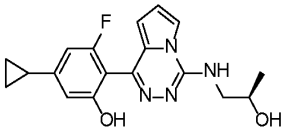
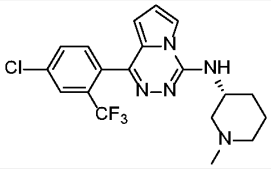
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-449		***
I-450		***
I-451		***
I-452		****
I-453		*****
I-454		***
I-455		*****
I-456		*****

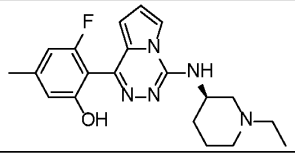
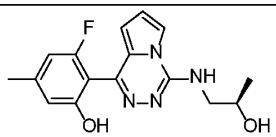
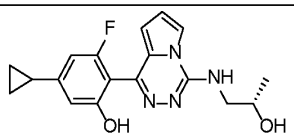
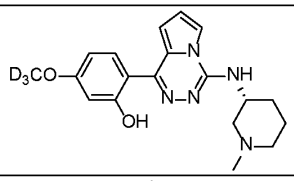
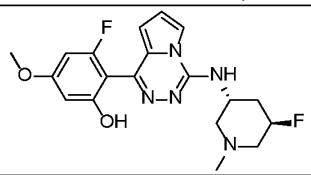
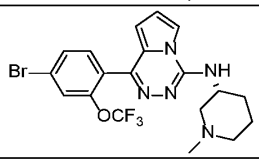
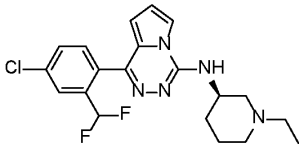
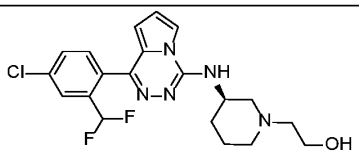
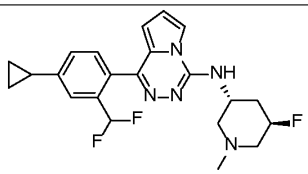
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-457		****
I-458		**
I-459		***
I-460		****
I-461		****
I-462		***
I-463		***
I-464		**

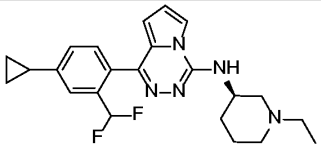
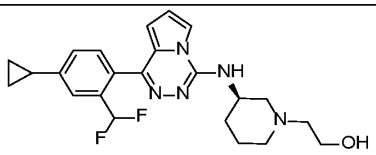
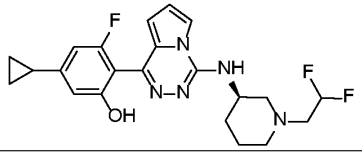
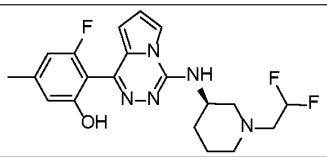
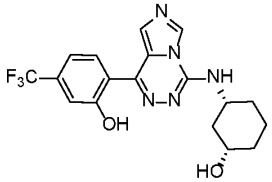
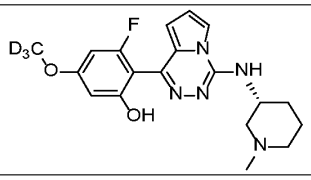
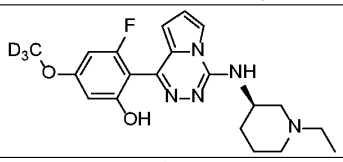
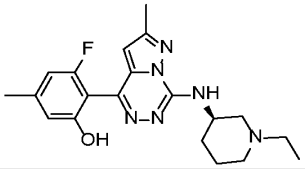
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-465		**
I-466		****
I-467		****
I-468		****
I-469		***
I-470		***
I-471		****
I-472		***

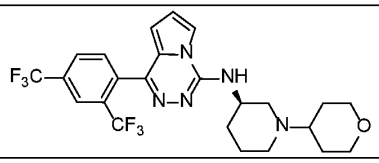
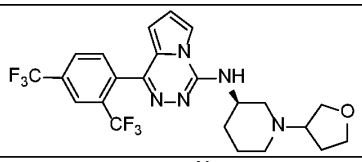
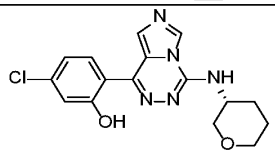
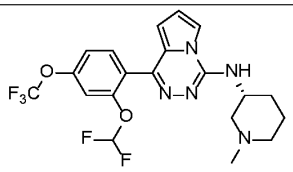
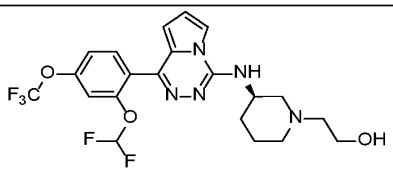
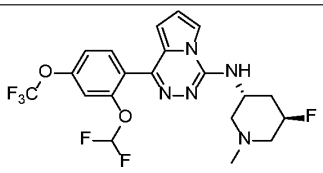
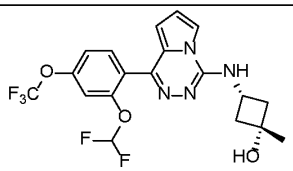
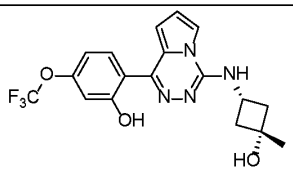
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-473		***
I-474		***
I-475		***
I-476		**
I-477		****
I-478		***
I-479		*****
I-480		****

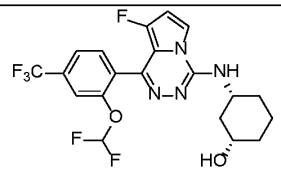
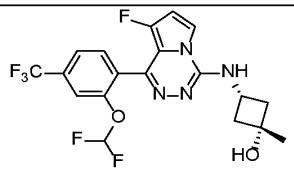
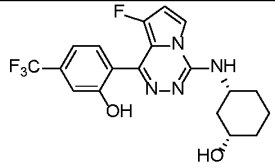
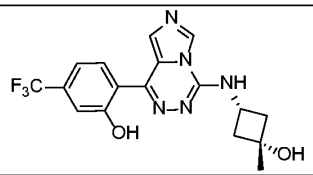
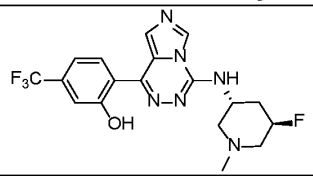
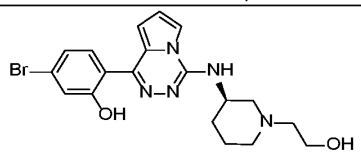
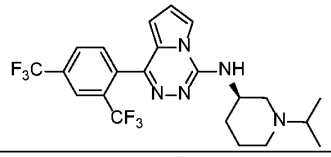
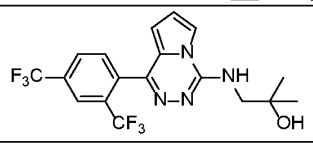
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-481		****
I-482		****
I-483		**
I-484		****
I-485		***
I-486		***
I-487		****
I-488		***

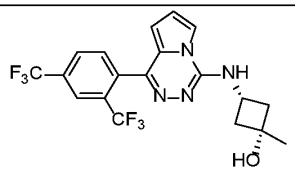
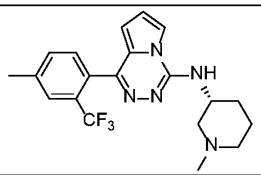
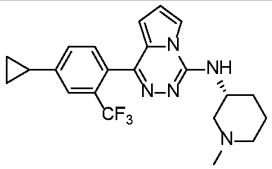
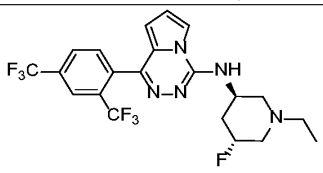
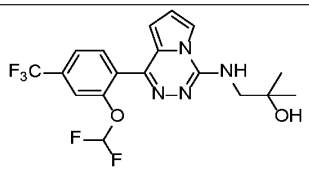
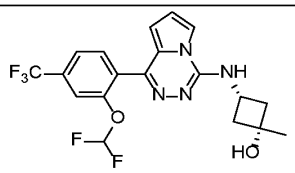
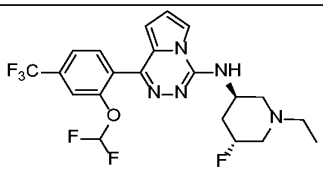
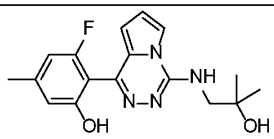
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-489		****
I-490		****
I-491		****
I-492		****
I-493		****
I-494		**
I-495		*****
I-496		***
I-497		****

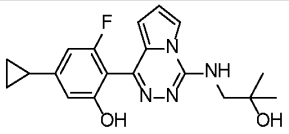
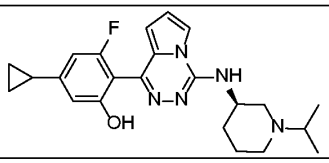
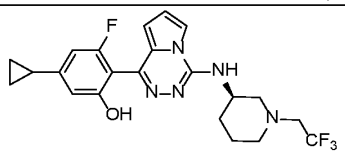
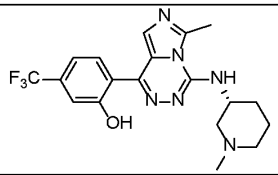
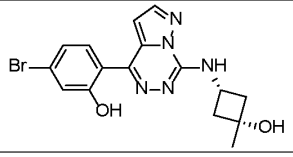
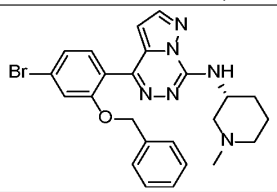
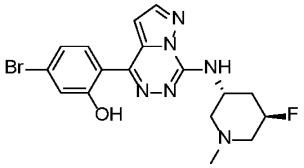
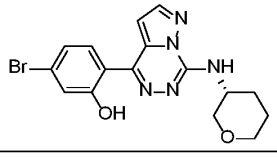
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-498		*****
I-499		***
I-500		***
I-501		*****
I-502		*****
I-504		*****
I-505		***
I-506		***
I-507		***

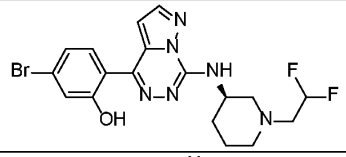
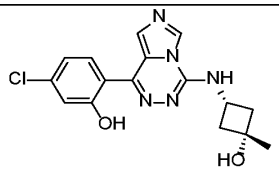
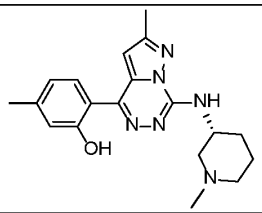
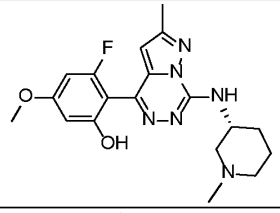
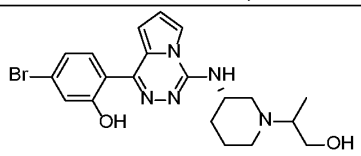
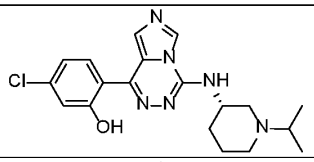
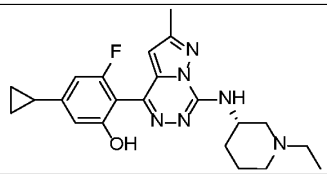
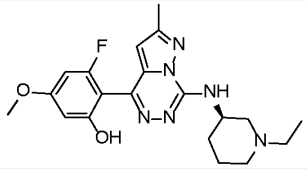
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-508		****
I-509		****
I-510		***
I-511		****
I-512		****
I-513		*****
I-514		*****
I-515		*****

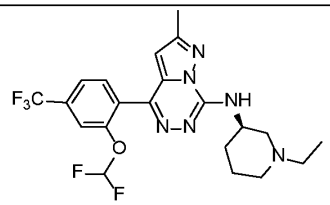
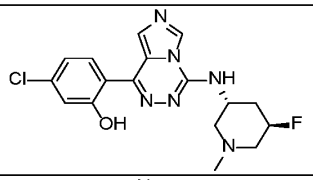
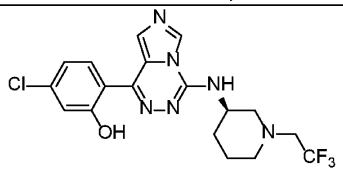
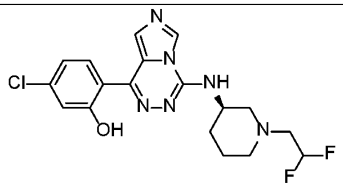
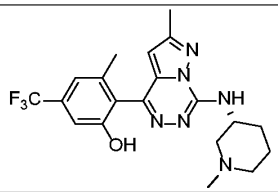
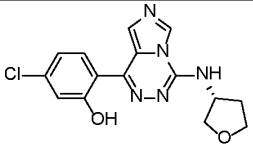
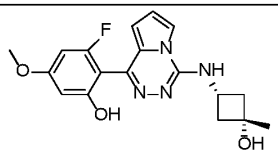
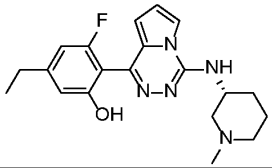
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-516		****
I-517		****
I-518		****
I-519		****
I-520		****
I-521		****
I-522		***
I-523		***

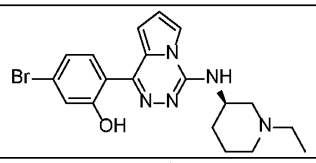
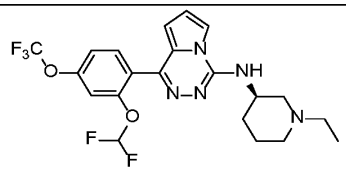
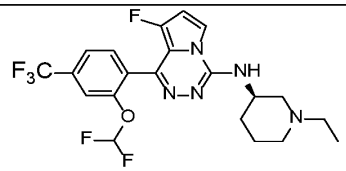
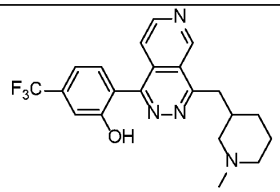
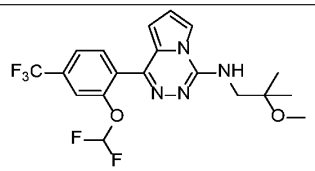
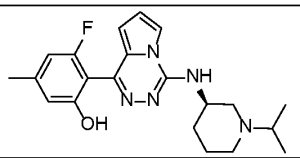
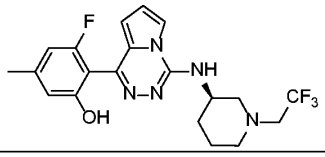
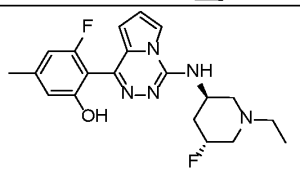
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-524		***
I-525		***
I-526		***
I-527		****
I-528		*****
I-529		****
I-530		*****
I-531		***

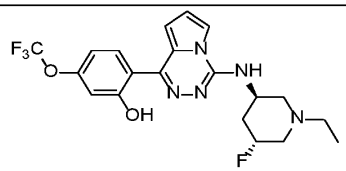
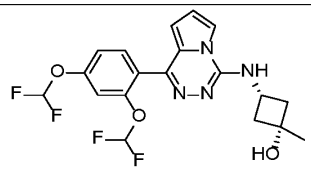
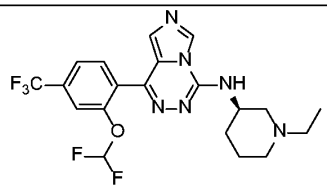
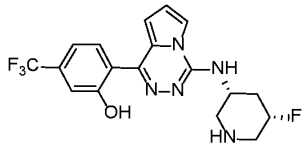
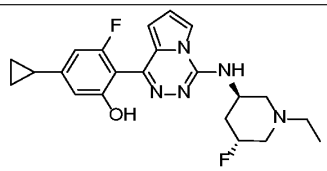
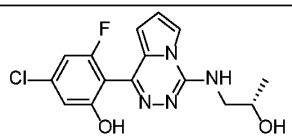
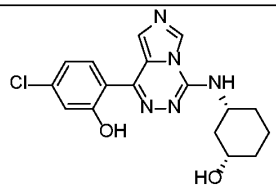
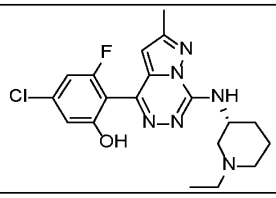
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-532		****
I-533		****
I-534		*****
I-535		****
I-536		***
I-537		****
I-538		****
I-539		****

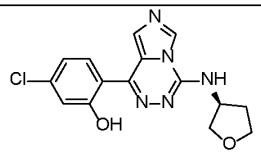
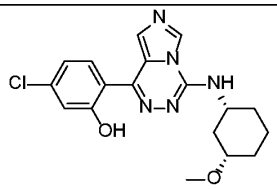
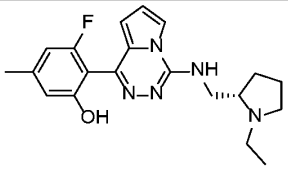
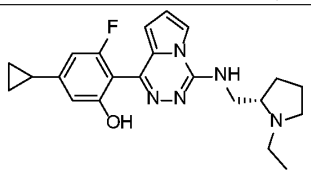
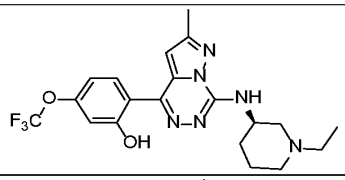
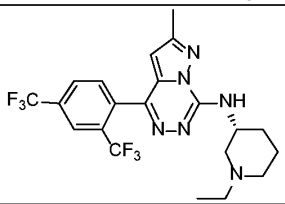
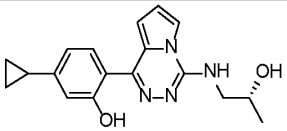
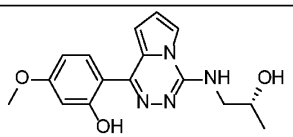
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-540		***
I-541		*****
I-542		***
I-543		*****
I-544		****
I-545		***
I-546		****
I-547		***

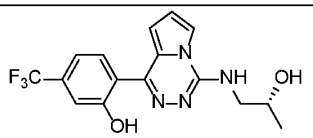
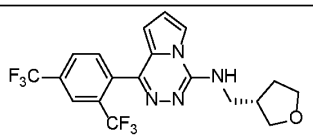
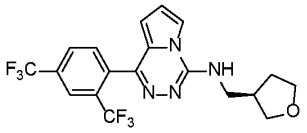
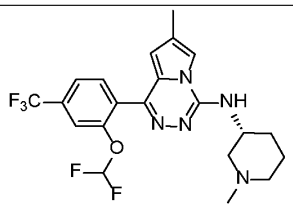
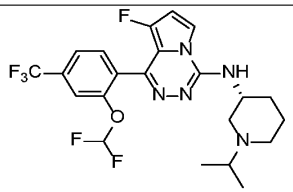
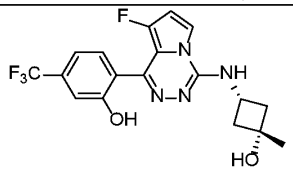
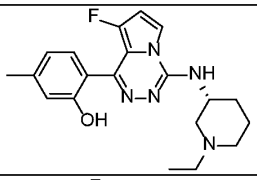
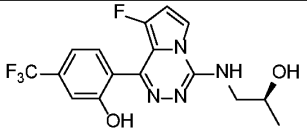
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-548		****
I-549		****
I-550		****
I-551		*****
I-552		****
I-553		*****
I-554		*****
I-555		*****

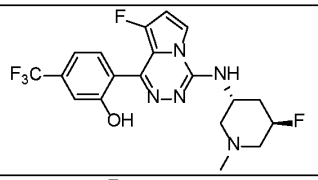
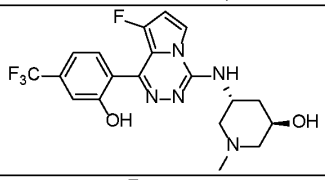
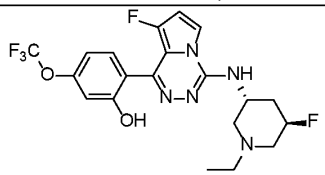
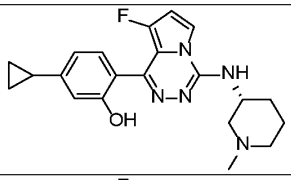
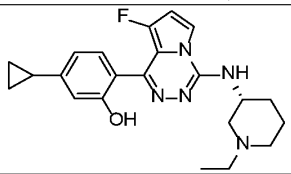
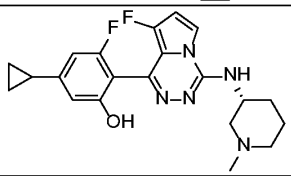
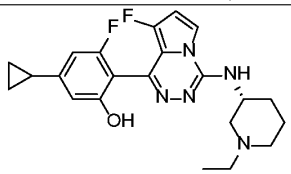
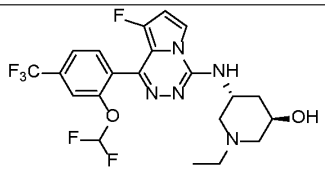
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-556		****
I-557		****
I-558		****
I-559		****
I-560		****
I-561		****
I-562		****
I-563		*****

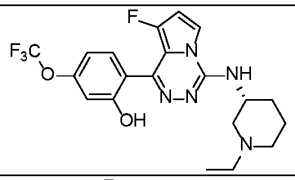
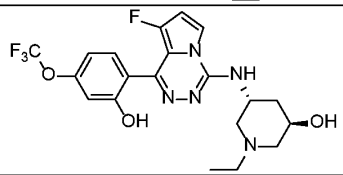
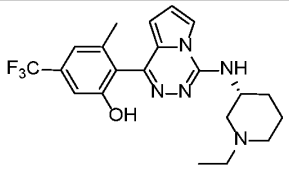
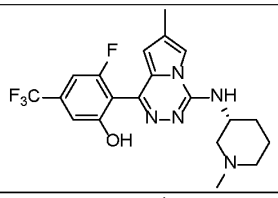
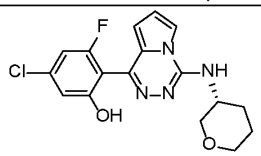
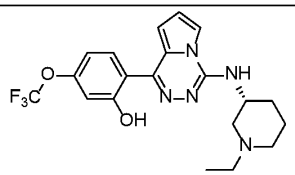
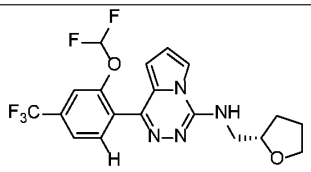
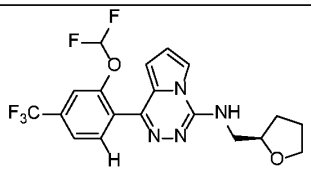
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-564		*****
I-565		****
I-566		****
I-567		***
I-568		****
I-569		*****
I-570		****
I-571		*****

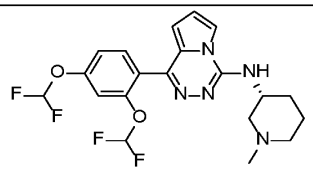
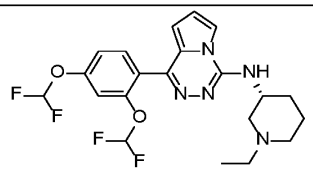
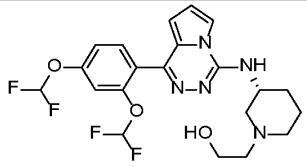
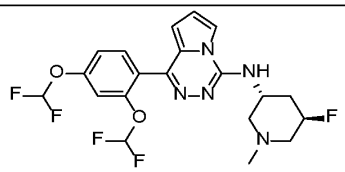
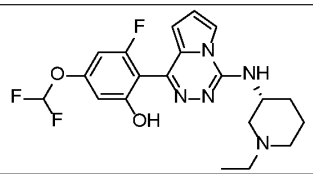
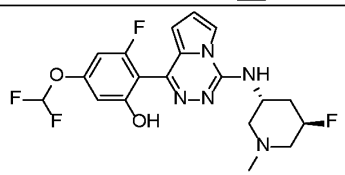
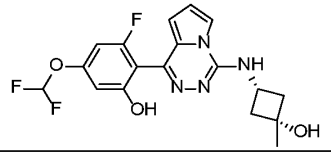
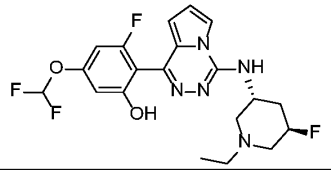
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-572		****
I-573		***
I-574		*****
I-575		**
I-576		*****
I-577		***
I-578		*****
I-579		*****

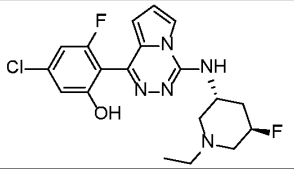
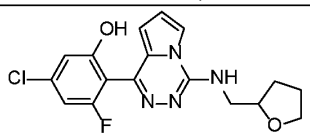
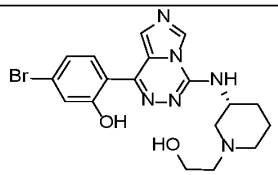
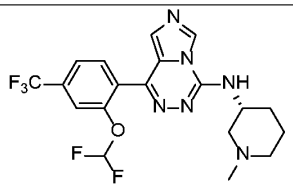
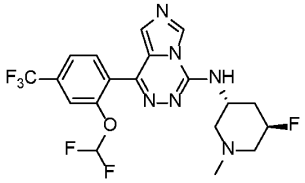
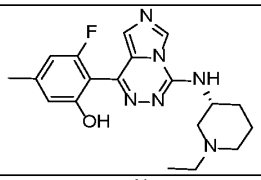
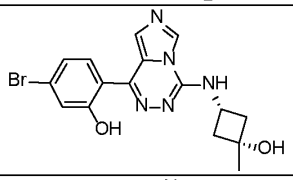
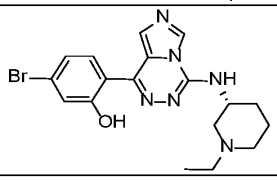
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-580		****
I-581		****
I-582		****
I-583		****
I-584		*****
I-585		****
I-586		**
I-587		***

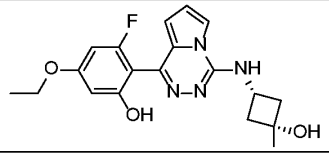
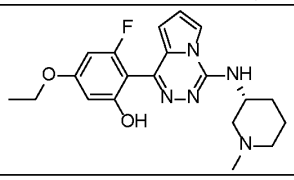
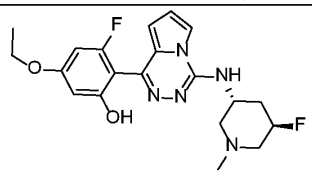
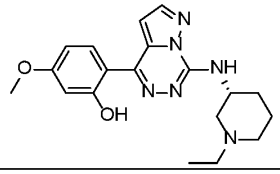
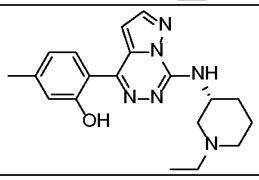
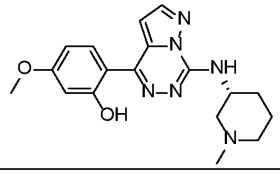
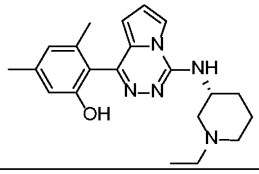
Compound Number	Structure	IC_{50} IL-1β Inhibition
I-588		***
I-589		***
I-590		***
I-591		****
I-592		*****
I-593		****
I-594		*****
I-595		***

Compound Number	Structure	IC_{50} IL-1β Inhibition
I-596		****
I-597		***
I-598		****
I-599		****
I-600		*****
I-601		*****
I-602		*****
I-603		**

Compound Number	Structure	IC_{50} IL-1β Inhibition
I-604		****
I-605		**
I-606		*****
I-607		*****
I-608		***
I-609		****
I-610		***
I-611		***

Compound Number	Structure	IC_{50} IL-1β Inhibition
I-612		****
I-613		****
I-614		****
I-615		***
I-616		*****
I-617		****
I-618		***
I-619		****

Compound Number	Structure	IC_{50} IL-1β Inhibition
I-620		****
I-621		***
I-623		*****
I-624		****
I-625		***
I-626		*****
I-627		****
I-628		*****

Compound Number	Structure	IC_{50} IL-1β Inhibition
I-629		***
I-630		****
I-631		***
I-632		****
I-633		****
I-634		***
I-636		*****

Without regard to whether a document cited herein was specifically and individually indicated as being incorporated by reference, all documents referred to herein are incorporated

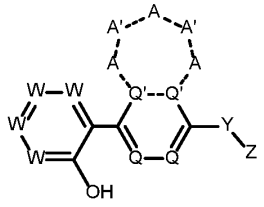
by reference into the present application for any and all purposes to the same extent as if each individual reference was fully set forth herein.

Although certain embodiments have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible in the embodiments without departing from the teachings thereof. All such modifications are intended to be encompassed within the scope of the claims presented herein.

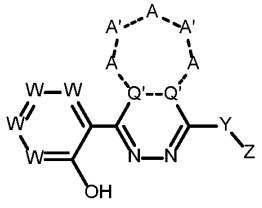
CLAIMS

What is Claimed is:

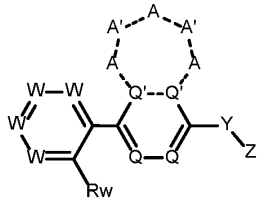
1. A compound having the structure of Formulae Ia, Ib, Ic, or Id:



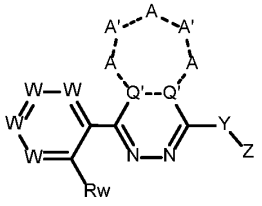
Ia



Ib



Ic



Id

wherein:

R_w is hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}8}$alkynyl, halogen, $C_{1\text{-}6}$alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, cyano, -NH_2, -$N(C_{1\text{-}6}alkyl)_2$, thiol, -SO_2NH_2, -$SO_2N(C_{1\text{-}6}alkyl)_2$, -$S(=O)(C_{1\text{-}6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$, $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each $C_{1\text{-}6}$alkyl, heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each Q is independently N or CH;

each Q' is independently N, C or CH;

each A is independently CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each A' is independently absent, CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each R_a is independently H, deuterium, halogen, -CN, -OH, -OR_2, =O, =N-OR_2, -SR_2, -$S(=O)R_2$, -$S(=O)_2R_2$, -$N(R_2)_2$, -$NR_2S(=O)(=NR_2)R^2$, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)OR_2$, -$OC(=O)OR_2$, -$C(=O)N(R_2)_2$, -$OC(=O)N(R_2)_2$, -$NR_2C(=O)R_2$, -$P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each---represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b}, or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, hydroxyC_{1-4}alkyl, C_{3-10}cycloalkyl, C_{2-7}heterocycloalkyl or aryl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

each R' is independently heterocyclyl, heteroaryl, aryl, C_{3-8}cycloalkyl, C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, halogen, hydroxy or cyano,

wherein each heterocycle, heteroaryl, C_{3-8}cycloalkyl and aryl are optionally substituted with 1, or 2 substituents each selected from R_3;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, C_{1-6}alkoxy, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl, C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, $(halo\text{-}C_{1-6}alkyl)_2$-amino, hydroxy-$C_{1-4}$alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-

amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

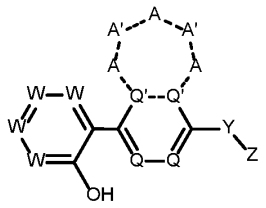
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

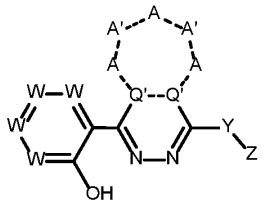
with the proviso that the compound is not Phenol, 5-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-2-[4-([1,1'-biphenyl]-4-yl-4-dibenzothienylamino)-1-naphthalenyl]; 5-[Phenyl(6-phenyl-4-dibenzothienyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzothienyl)amino]-1-naphthalenyl]phenol; 5-[2-Dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-

dibenzothienyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-[2-Dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-2-[4-[2-dibenzofuranyl(9,9-dimethyl-9H-fluoren-2-yl)amino]-1-naphthalenyl]phenol; 5-(4-Dibenzofuranylphenylamino)-2-[4-(4-dibenzofuranylphenylamino)-1-naphthalenyl]phenol; 5-(4-Dibenzofuranyl-2-naphthalenylamino)-2-[4-(4-dibenzofuranyl-2-naphthalenylamino)-1-naphthalenyl]phenol; 5-[Phenyl(6-phenyl-4-dibenzofuranyl)amino]-2-[4-[phenyl(6-phenyl-4-dibenzofuranyl)amino]-1-naphthalenyl]phenol; 5-([1,1′-Biphenyl]-2-yl-4-dibenzofuranylamino)-2-[4-([1,1′-biphenyl]-2-yl-4-dibenzofuranylamino)-1-naphthalenyl]phenol; 4-[4-(4-Dibenzofuranylphenylamino)-1-naphthalenyl]-2′,3′,5′,6′-tetrafluoro-4′-(2-naphthalenylphenylamino)[1,1′-biphenyl]-3-ol; 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]phenol; or 2-[4-[[6-[[3-(2-Amino-4-pyrimidinyl)-2-pyridinyl]oxy]-3-pyridinyl]amino]-1-phthalazinyl]-4-fluorophenol; wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

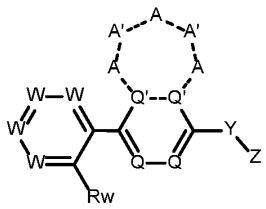
2. The compound of claim 1 having the structure of Formulae IIa, IIb, IIc, or IId:



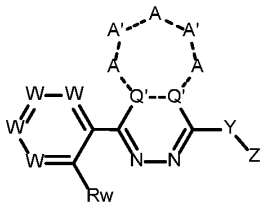
IIa



IIb



IIc



IId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ and $S(=O)_2N(R_{1b})_2$, wherein each C_{1-6}alkyl, heterocycle, heteroaryl and aryl are optionally substituted with 1or 2 substituents each selected from R_5;

each W is independently CH, CR', or N, wherein at least one Q' is N;

each Q is independently N or CH;

each Q' is independently N, C or CH;

each A is independently CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each A' is independently absent, CH, CH_2, CR_a, CHR_a, CR_4, CHR_4, N, NH, NR_a, NR_4, S, or O;

each R_a is independently H, deuterium, halogen, -CN, -OH, $-OR_2$, =O, =N-OR_2, $-SR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-N(R_2)_2$, $-NR_2S(=O)(=NR_2)R^2$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)OR_2$, $-OC(=O)OR_2$, $-C(=O)N(R_2)_2$, $-OC(=O)N(R_2)_2$, $-NR_2C(=O)R_2$, $-P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each-- represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino hydroxyC_{1-4}alkyl, C_{3-10}cycloalkyl, C_{2-7}heterocycloalkyl or aryl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

each R' is independently heterocyclyl, heteroaryl, aryl, C_{3-8}cycloalkyl, C_{1-4}alkyl, C_{1-4}alkoxy, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, halogen, hydroxy or cyano,

wherein each heterocycle, heteroaryl, C_{3-8}cycloalkyl and aryl are optionally substituted with 1, or2, substituents each selected from R_3;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, C_{1-6}alkoxy, $NH(_{1-6}alkyl)$, $NH(C_{1-6}alkoxy)$ wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}

hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl, C_{3-10}cycloalkyl a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-$C_{1-6}alkyl)_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, $(C_{1-4}alkyl\text{-}amino)_2$-$C_{1-4}$alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, $_{1-4}$alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or$_2$substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

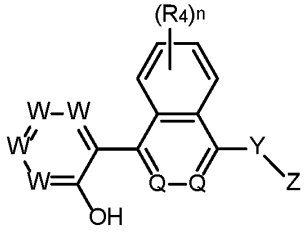
wherein heterocyclyl is a saturated or partially unsaturated$_{3-6}$membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5; and

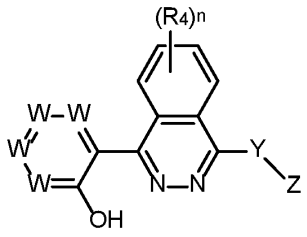
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

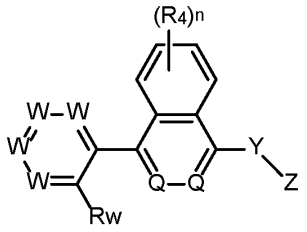
3. The compound of claim 1 having the structure of Formulae IIIa, IIIb, IIIc, or IIId:



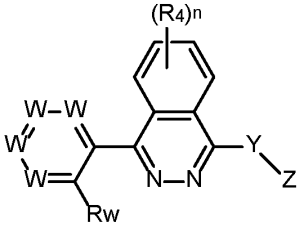
IIIa



IIIb



IIIc



IIId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$,

$NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ and $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each Q is independently N, or CH;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxyC_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-6}alkyl)_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl,

C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino-C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R' and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S,

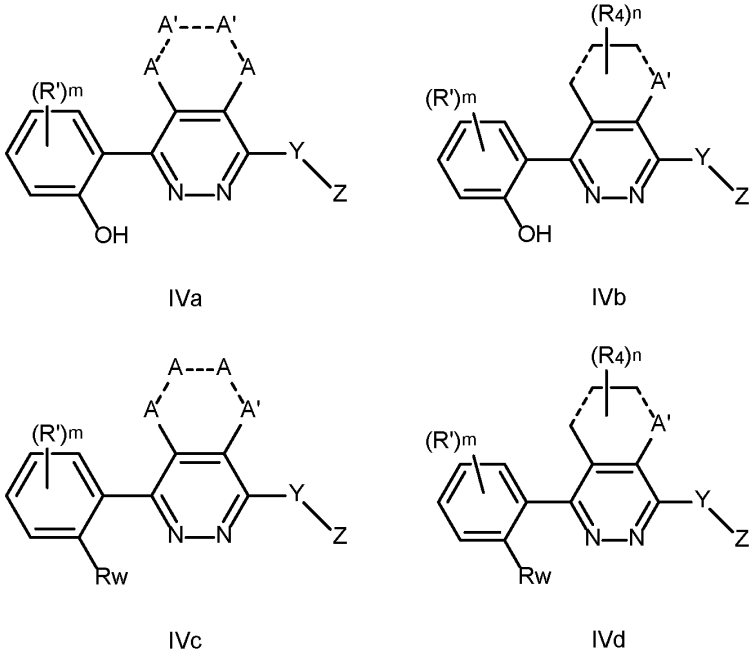
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

n is 0, 1, or 2;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

4. The compound of claim 1 having the structure of Formulae IVa, IVb, IVc, or IVd:



IVa IVb

IVc IVd

wherein:

R_w is H, $C_{1\text{-}6}$alkyl, $C_{2\text{-}8}$alkynyl, halogen, $C_{1\text{-}6}$alkoxy, halo-$C_{1\text{-}4}$alkyl, halo-$C_{1\text{-}4}$alkoxy, cyano, -NH_2, -$N(C_{1\text{-}6}alkyl)_2$, thiol, -SO_2NH_2, -$SO_2N(C_{1\text{-}6}alkyl)_2$, -S(=O)($C_{1\text{-}6}$alkyl), cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each A is independently NH, S, O, CH_2, or CR_4;

A' is independently NH, S, O, CH_2, CR_4 or absent;

Each ----represents either an absent, single, or double bond;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

R_{1a} is hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxyC_{1-4}alkyl;

R_{1b} is hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocycle, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

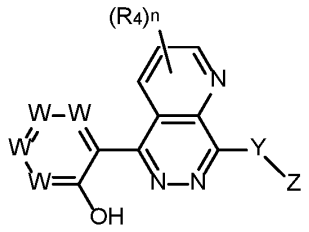
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

m is 0, 1, 2, 3, or 4; and

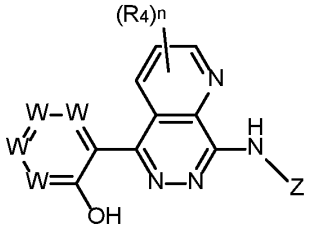
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

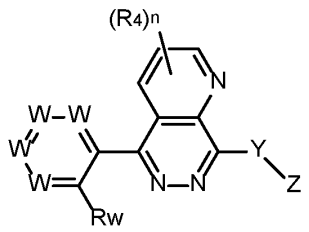
5. The compound of claim 1 having the structure of Formulae Va, Vb, Vc, or Vd:



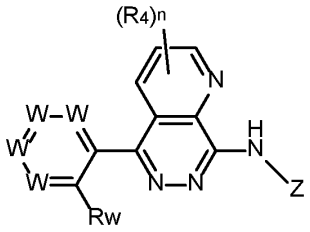
Va



Vb



Vc



Vd

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, -NH_2, -N(C_{1-6}alkyl)$_2$, thiol, -SO_2NH_2, -SO_2N(C_{1-6}alkyl)$_2$, -S(=O)(C_{1-6}alkyl), cycloalkyl, CHR_{1a}, (C=O)R_{1a}, OR_{1a}, N(R_{1b})$_2$, S(=O)R_{1a}, S(=O)$_2R_{1a}$, O(C=O)R_{1a}, (C=O)OR_{1a}, NR_{1b}(C=O)R_{1b}, (C=O)NHR_{1b}, (C=O)N(R_{1b})$_2$ NR_{1b}(C=O)OR_{1a}, O(C=O)N(R_{1b})$_2$, ONR_{1b}(C=NR_{1b})NR_{1b}, NR_{1b}S(=O)$_2R_{1a}$ or S(=O)$_2$N(R_{1b})$_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR', or N;

Y is C(R_{1a})$_2$, C=O, O, NR_{1b} or a bond;

R_{1a} is hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxyC_{1-4}alkyl;

R_{1b} is hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein

heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system,

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R'and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-4}alkyl)$_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

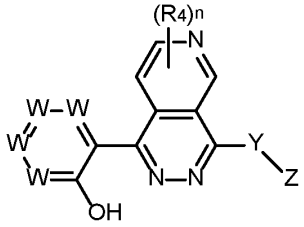
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

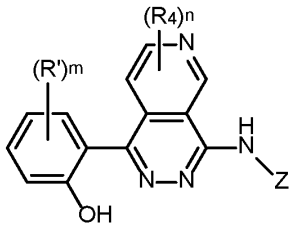
n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

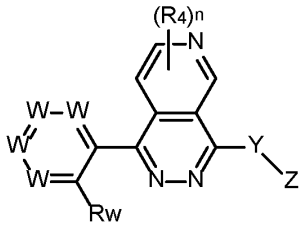
6. The compound of claim 1 having the structure of Formulae VIa, VIb, VIc, or VId:



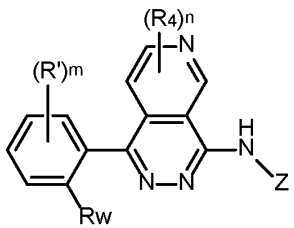
VIa



VIb



VIc



VId

wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)NHR_{1b}$,

$ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR', or N;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxyC_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, $-CO_2H$, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

each R'and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

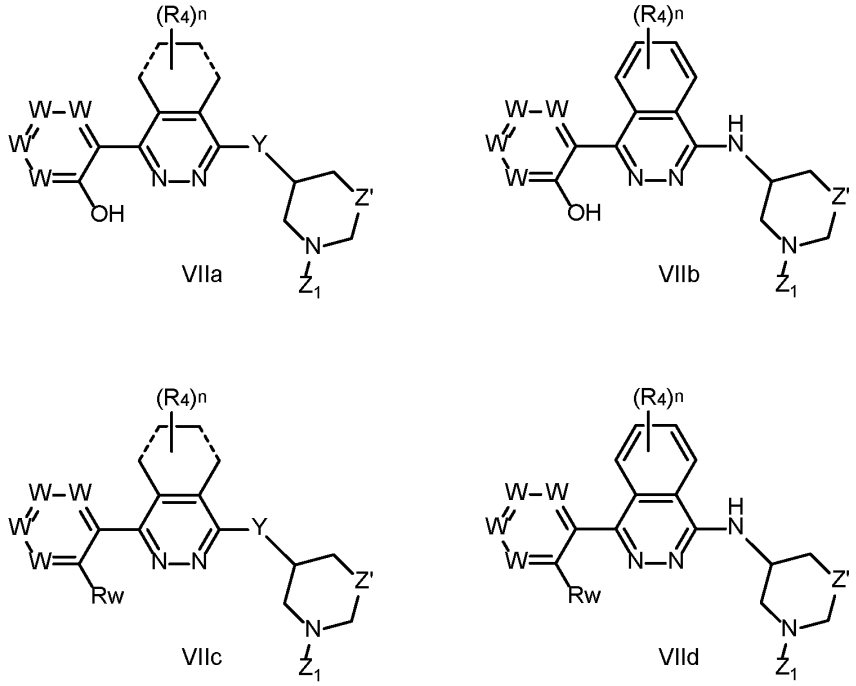
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

7. The compound of claim 1 having the structure of Formulae VIIa, VIIb, VIIc, or VIId:



wherein:

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each -- represents either an absent, single, or double bond;

each Z' is independently CH_2 or absent;

Y is $C(R_{1a})_2$, C=O, O, NR_{1b} or a bond;

each R_{1a} is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino or hydroxyC_{1-4}alkyl;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl; and

each Z_1, R', and R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkylamino, $(C_{1-4}alkyl)_2$amino, C_{1-4}alkoxy, halo-C_{14}alkoxy, heteroaryl, heterocyclyl, and phenyl,

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

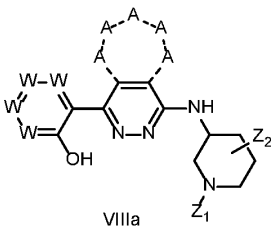
wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

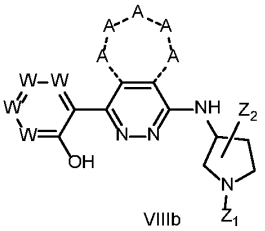
R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

n is 0, 1, 2, or 3;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

8. The compound of claim 1 having the structure of Formulae VIIIa, VIIIb, VIIIc, VIIId, VIIIXe, or VIIIf:


VIIIa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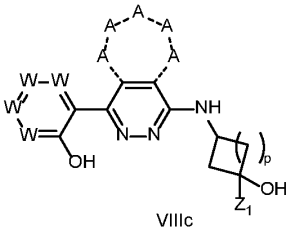
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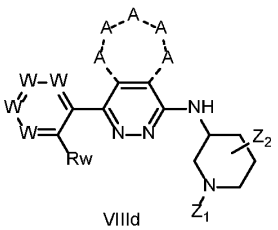
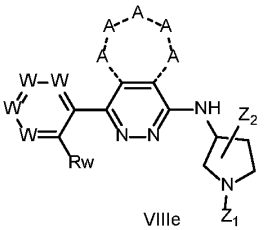
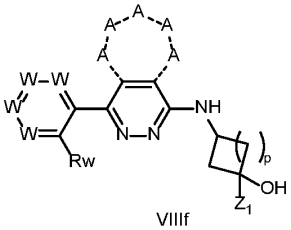

VIIId


VIIIe


VIIIf

wherein

R_w is hydrogen, C_{1-6}alkyl, C_{2-8}alkynyl, halogen, C_{1-6}alkoxy, halo-C_{1-4}alkyl, halo-C_{1-4}alkoxy, cyano, $-NH_2$, $-N(C_{1-6}alkyl)_2$, thiol, $-SO_2NH_2$, $-SO_2N(C_{1-6}alkyl)_2$, $-S(=O)(C_{1-6}alkyl)$, cycloalkyl, CHR_{1a}, $(C=O)R_{1a}$, OR_{1a}, $N(R_{1b})_2$, $S(=O)R_{1a}$, $S(=O)_2R_{1a}$, $O(C=O)R_{1a}$, $(C=O)OR_{1a}$, $NR_{1b}(C=O)R_{1b}$, $(C=O)NHR_{1b}$, $(C=O)N(R_{1b})_2$ $NR_{1b}(C=O)OR_{1a}$, $O(C=O)N(R_{1b})_2$, $ONR_{1b}(C=NR_{1b})NR_{1b}$, $NR_{1b}S(=O)_2R_{1a}$ or $S(=O)_2N(R_{1b})_2$, wherein each heterocycle, heteroaryl and aryl are optionally substituted with 1 or 2 substituents each selected from R_5;

each W is independently CH, CR' or N;

each A is independently absent, CH, CH_2, CR_a, CHR_a, N, NH, NR_a, S, or O;

each R_a is independently H, deuterium, halogen, -CN, -OH, $-OR_2$, =O, =N-OR_2, $-SR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-N(R_2)_2$, $-NR_2S(=O)(=NR_2)R^2$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)OR_2$, $-OC(=O)OR_2$, $-C(=O)N(R_2)_2$, $-OC(=O)N(R_2)_2$, $-NR_2C(=O)R_2$, $-P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}alkyl)_2$, halo-C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl;

each-- represents either an absent, single, or double bond;

p is 0, 1, 2, 3 or 4;

each Z_1, Z_2, R_2, R' or R_4 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, heteroaryl, heterocyclyl, and phenyl;

wherein heteroaryl is a 5-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members selected from N, O, and S,

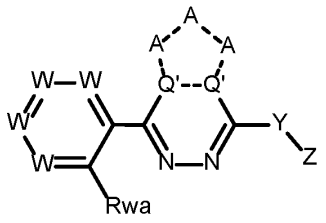
wherein heterocyclyl is a saturated or partially unsaturated 3-6 membered monocyclic or 9-10 membered bicyclic ring system having 1, 2, or 3 heteroatom ring members selected from N, O, and S, and

wherein each instance of phenyl, heteroaryl or heterocyclyl is optionally substituted with 1, or 2 substituents each selected from R_5;

R_5 is independently selected from halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkylamino, $(C_{1-4}alkyl)_2$amino, aminoC_{1-4}alkyl, hydroxylC_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

9. The compound of claim 2 having the structure of Formula IX



IXa

wherein:

each W is independently CH, CR' or N;

each Q' is independently N, or C, wherein at least one Q' is N;

each A is independently CH, CH_2, CR_a, CR_4, N, NH or NR_4;

Y is NR_{1b} or a bond;

Each R_{wa} is hydrogen, hydroxyl, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy,

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, (C_{1-6}alkyl)$_2$-amino, halo-C_{1-4}alkyl-amino, (halo-C_{1-6}alkyl)$_2$-amino, hydroxy-C_{1-4}alkyl-amino, C_{1-4}alkoxy-C_{1-4}alkyl-amino, amino-C_{1-4}alkyl, C_{1-4}alkyl-amino-C_{1-4}alkyl, (C_{1-4}alkyl-amino)$_2$-C_{1-4}alkyl, C_{1-4}alkoxy, halo-C_{1-4}alkoxy, hydroxy-C_{1-4}alkoxy, C_{1-4}alkyl-C_{1-4}alkoxy, C_{3-10}cycloalkyl, C_{3-10}cycloalkyl-amino, C_{3-10}cycloalkyl-amino-C_{1-4}alkyl, heteroaryl-C_{1-4}alkyl, heteroaryl-amino, heteroaryl-C_{1-4}alkyl-amino, heterocyclyl, heterocyclyl-C_{1-4}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{1-4}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{3-10}cycloalkyl, phenyl, and phenyl-C_{1-4}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, or S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system,

wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3;

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

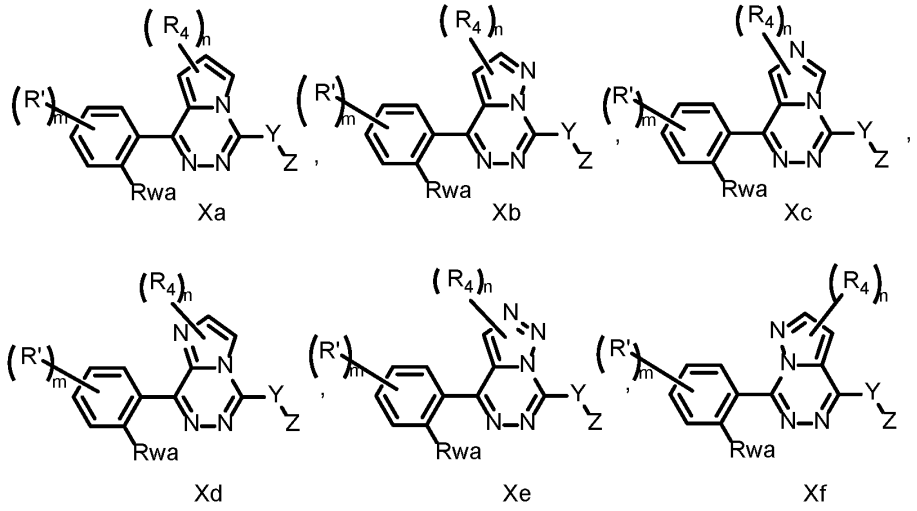
R' is selected from H, substituted or unsubstituted cycloalkyl, halo-C_{1-4}alkyl, haloalkoxy, halogen, C_{1-6} alkoxy, cyano, hydroxyC_{1-4}alkyl or aryl optionally substituted by C_{1-4}alkyl;

each R_a is independently H, deuterium, halogen, -CN, -OH, -OR_2, =O, =N-OR_2, -SR_2, -$S(=O)R_2$, -$S(=O)_2R_2$, -$N(R_2)_2$, -$NR_2S(=O)(=NR_2)R^2$, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)OR_2$, -$OC(=O)OR_2$, -$C(=O)N(R_2)_2$, -$OC(=O)N(R_2)_2$, -$NR_2C(=O)R_2$, -$P(=O)(R_2)_2$, C_{1-4}alkyl, $(C_{1-4}$alkyl$)_2$, halo- C_{1-6}alkyl, C_{1-6}heteroalkyl, C_{3-8}cycloalkyl, C_{2-7}heterocycloalkyl, aryl or monocyclic heteroaryl; and

R_4 is independently selected from halogen, hydroxyl, cyano, or C_{1-4}alkyl;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

10. The compound of claim 9 having the structure of Formulae Xa, Xb, Xc, Xd, Xe or Xf:



Wherein:

each R_{wa} is hydrogen, hydroxyl, C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkoxy, or halo-C_{1-4}alkoxy

R' is selected from hydrogen, halogen, hydroxyl, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxyC_{1-4}alkyl , C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl; and

R_4 is selected from hydrogen, C_{1-4} alkyl, halogen and halo-C_{1-4}alkyl;

Y is NR_{1b} or a bond;

each R_{1b} is independently hydrogen, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl or hydroxyC_{1-4}alkyl; and

each Z is heterocyclyl, heteroaryl, aryl, C_{3-10}cycloalkyl, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, hydroxy-C_{1-8}alkyl, NH(hydroxy-C_{1-6}alkyl), NH(C_{1-6}alkoxy) wherein each Z is optionally substituted with OH, NH_2, -CO_2H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6} hydroxyalkyl, C_{2-6}acyl, C_{2-6}alkanoic acid, C_{2-6}alkanoate ester, or heterocyclyl, and wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S, each optionally substituted with 1, 2, 3, 4, or 5 substituents each selected from R_2;

R_2 is independently selected from halogen, hydroxy, cyano, C_{14}alkyl, hydroxy-C_{14}alkyl, deuterium-C_{14}alkyl, halo-C_{14}alkyl, amino, C_{14}alkylamino, $(C_{16}alkyl)_2$amino, halo-C_{14}alkylamino, $(halo\text{-}C_{16}alkyl)_2$amino, hydroxy-$C_{14}$alkylamino, C_{14}alkoxy-C_{14}alkyl-amino, aminoC_{14}alkyl, C_{14}alkylaminoC_{14}alkyl, $(C_{14}alkylamino)_2C_{14}$alkyl, C_{14}alkoxy, halo-C_{14}alkoxy, hydroxy-C_{14}alkoxy, C_{14}alkyl-C_{14}alkoxy, C_{310}cycloalkyl, C_{310}cycloalkyl-amino, C_{310}cycloalkyl-amino-C_{14}alkyl, heteroarylC_{14}alkyl, heteroarylamino, heteroarylC_{14}alkyl-amino, heterocyclyl, heterocyclyl-C_{14}alkyl, heterocyclyl-amino, heterocyclyl-amino-C_{14}alkyl, heterocyclyl-C_{1-4}alkoxy, heterocyclyl-amino- C_{310}cycloalkyl, phenyl, and phenyl-C_{14}alkoxy,

wherein heteroaryl is a 5-6 membered monocyclic or 6-10 membered bicyclic ring system having 1, 2, 3, or 4 heteroatom ring members independently selected from N, O, and S,

wherein heterocyclyl is a saturated or partially unsaturated 3-7 membered monocyclic, 6-10 membered bicyclic or 13-16 membered polycyclic ring system having 1, 2, or 3 heteroatom ring members independently selected from N, O, and S,

wherein C_{3-10}cycloalkyl is a saturated or partially unsaturated 3-7 membered monocyclic ring system, and

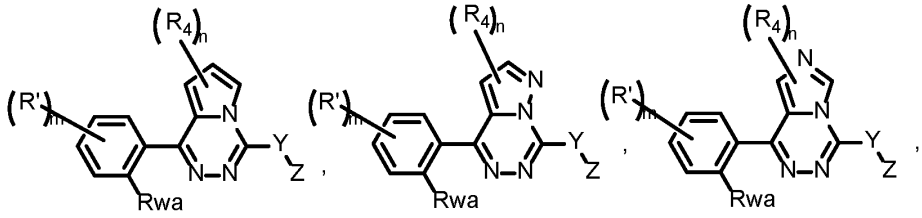
wherein each instance of phenyl, heteroaryl, heterocyclyl, or C_{3-10}cycloalkyl is optionally substituted with 1 or 2 substituents each selected from R_3; and

R_3 is independently selected from halogen, hydroxyl, cyano, C_{1-4}alkyl, deuterium-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkoxy, and halo-C_{1-4}alkoxy;

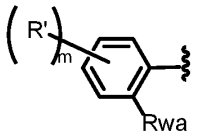
m is 1, 2, 3, 4, or 5; and

n is 0, 1, 2, or 3;

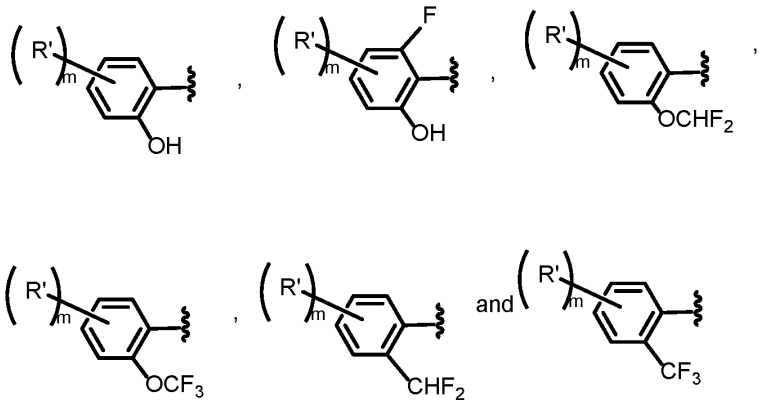
11. The compound of claim 10 having the structure of Formulae XIa, XIb, XIc:



XIa XIb XIc

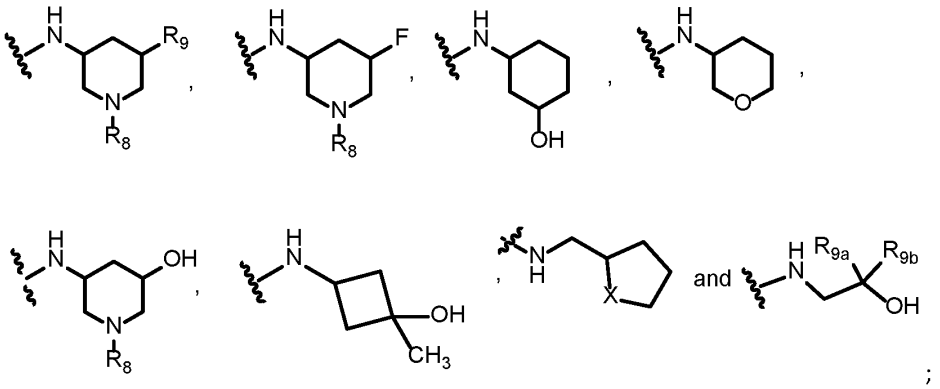
wherein the moiety having the structure  is selected from:

;



R' is selected from halogen, hydroxy, cyano, nitro, C_{1-4}alkyl, deutero-C_{1-4}alkyl, halo-C_{1-4}alkyl, amino, C_{1-4}alkyl-amino, $(C_{1-4}alkyl)_2$-amino, amino-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkyl-carbonyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halo-C_{1-4}alkoxy, and C_{3-10}cycloalkyl;

Y and Z when taken together is selected from:



R_4 is selected from hydrogen, C_{1-4} alkyl, halogen and halo-C_{1-4}alkyl;

R_8 is selected from C_{1-4}alkyl, CH_2CH_2OH, $CH_2CH_2OCF_3$, $CH_2CH_2OCHF_2$, and $CH_2CH_2C(CH_3)_2OH$;

R_9, R_{9a}, R_{9b} is selected from hydrogen or C_{1-4}alkyl or C_{3-6}cycloalkyl; and C_{9a} and C_{9b} can optionally cyclized to form a 3-6 membered ring.

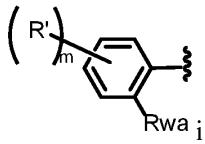
m is 1, 2, 3, 4, or 5.

n is 0, 1, 2, or 3.

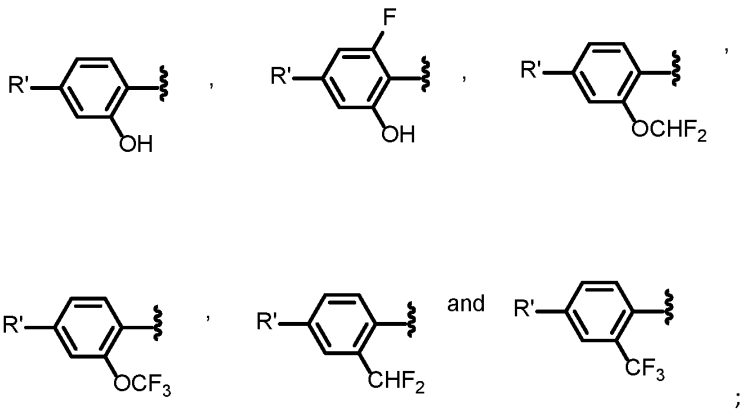
X is selected from O or NR_8; and

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

12. The compound of claim 11, wherein the moiety having the structure:



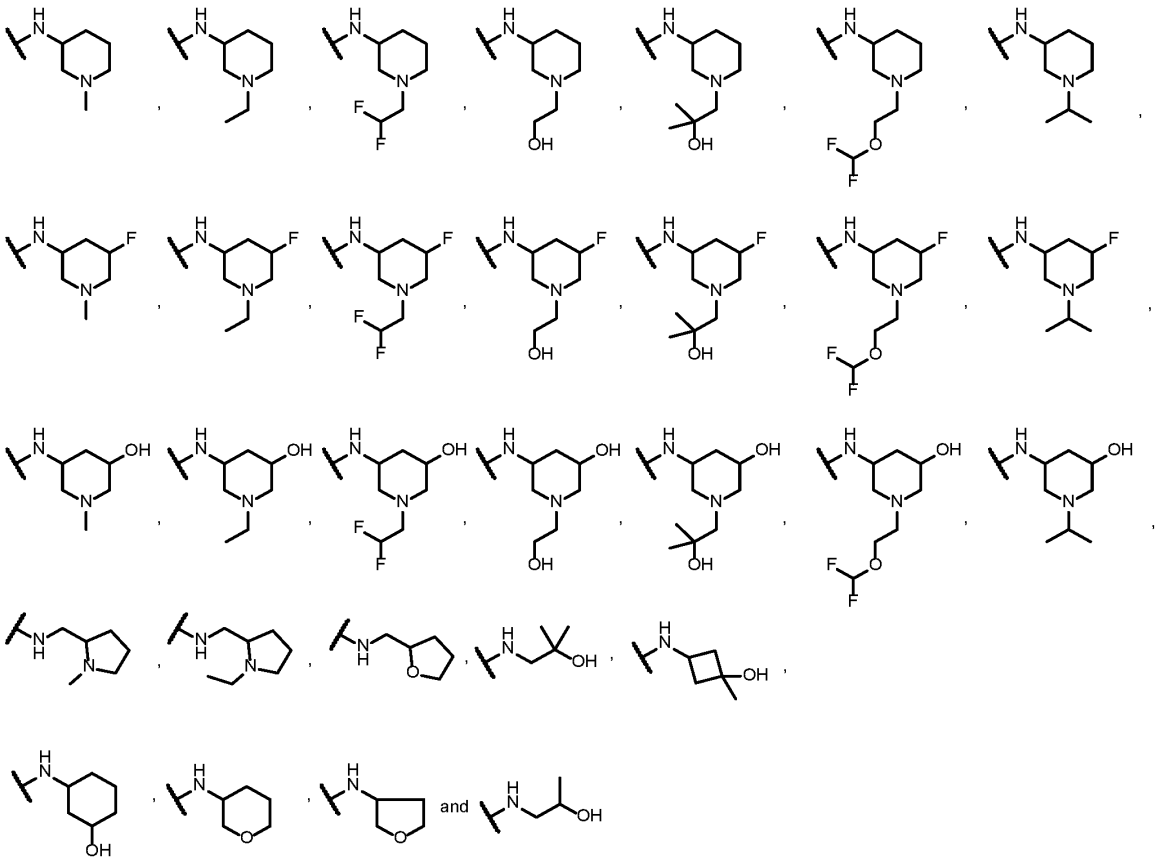
is selected from:



;

wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

13. The compound of claim 12, wherein Y and Z when taken together is selected from:



; wherein a form of the compound is selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, tautomer, and isotope enriched form thereof.

14. A compound or form thereof, selected from the group consisting of:

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}thieno[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol;

2-{4-[(pyrrolidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)benzene-1,3-diol;

5-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

4-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-methyl-4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

3-hydroxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)benzonitrile;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpyrrolidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-fluoro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]oxy}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(piperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-(5-methyl-1,2,4-thiadiazol-3-yl)-2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1H-1,2,3-triazol-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(5-methyl-1,2,4-thiadiazol-3-yl)phenol;

4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)[1,1'-biphenyl]-3-ol;

3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)[1,1'-biphenyl]-4-ol;

4,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2,3-dimethyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(1-methylpiperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(7,7-dimethyl-4-{[(3R)-piperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7,7-dimethyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{methyl[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-fluoro-3-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(5,6-dihydro-2H-pyran-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol;

2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-(3,6-dihydro-2H-pyran-4-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(2,5-dihydrofuran-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-(1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-chloro-2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(oxolan-3-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol;

1-[3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]ethan-1-one;

ethyl [(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-methoxy-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

4-hydroxy-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridine-2-carbonitrile;

3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-6-(trifluoromethyl)pyridin-2-ol;

2-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-cyclopropyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-methyl-3-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-2-ol;

5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-2-(trifluoromethyl)pyridin-4-ol;

6-hydroxy-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridine-2-carbonitrile;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

2-methyl-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

4-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-3-ol;

3-hydroxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(pyrrolidin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methyl-1H-pyrrol-3-yl)phenol;

2-{4-[(1-methylazepan-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]methyl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]methyl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

[(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetic acid;

5-methyl-2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)phenol;

2-{1-[(piperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(1-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethoxy)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-chloro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methylpyrrolidin-3-yl)phenol;

2-(4-{[2-(morpholin-4-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(azetidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol;

2-[1-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[2-(piperidin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-[1-(4-methylpiperazin-1-yl)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol;

2-(4-methyl-5-{[(3R)-1-methylpiperidin-3-yl]amino}-3,4-dihydro-2H-pyridazino[4,5-b][1,4]oxazin-8-yl)-5-(trifluoromethyl)phenol;

2-{1-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

4-[2-amino-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]methanesulfonamide;

4-[2-(methylamino)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]acetamide;

4-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-(4-chloro-2-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)benzonitrile;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

1-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(2H-1,2,3-triazol-2-yl)phenol;

1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-chloro-2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-hydroxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

3,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-chloro-3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-N-[(3R)-1-methylpiperidin-3-yl]-1H-pyrazolo[3,4-d]pyridazin-7-amine;

1-[2-(2,5-dihydrofuran-3-yl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(1-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}-1H-pyrazolo[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

2-[4-({2-[(3R)-3-methylmorpholin-4-yl]ethyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

2-[4-({2-[(3S)-3-methylmorpholin-4-yl]ethyl}amino)phthalazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[2-(piperazin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(azetidin-2-yl)methyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

2-{1-[3-(dimethylamino)piperidin-1-yl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-(piperazin-1-yl)pyrido[3,4-d]pyridazine;

2-(1-methyl-8-{[(3R)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(1-methyl-8-{[(3S)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzene-1-sulfonamide;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-[4-cyclopropyl-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-methyl-5-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)pyridin-4-ol;

4-(2-methoxy-6-methylpyridin-3-yl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

2-(4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

1-{4-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}-N,N-dimethylpiperidin-3-amine;

2-amino-3-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

4-(2,3-difluoro-4-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

3-(difluoromethoxy)-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-[2-(difluoromethoxy)-3-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzene-1-sulfonamide;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-3-ol;

1-[2-(methoxymethoxy)-4-(1,3-oxazol-2-yl)phenyl]-N-[(3S)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3S)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(1,3-oxazol-2-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(difluoromethoxy)-5-fluoro-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-{4-[(1-methyl-1H-pyrazol-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzamide;

5-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-8-amine;

8-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-5-amine;

2-{1-[(1-methylazepan-3-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-{2-[(oxetan-3-yl)oxy]-4-(trifluoromethyl)phenyl}pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenyl]methanol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(methanesulfonyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-cyclopropyl-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)pyridin-3-ol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(4-chloro-2-fluoro-6-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-azabicyclo[2.2.2]octan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(pyrimidin-2-yl)phenol;

1-{4-[2-methoxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}-N,N-dimethylpiperidin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[5-(trifluoromethyl)[1,1'-biphenyl]-2-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{3-[(dimethylamino)methyl]pyrrolidin-1-yl}phthalazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-(trifluoromethyl)pyridin-3-yl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-(2,4,6-trimethylphenyl)pyrido[3,4-d]pyridazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2,4-di(propan-2-yl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-(3-cyclopropyl-6-fluoro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

6-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

6-chloro-3-fluoro-2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)phenol;

2-{4-[(4-methyl-4-azaspiro[2.5]octan-7-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-cyclobutylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(2,4-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-methyl-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile;

1-(4-chloro-2,6-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-cyclopropylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2,2,2-trifluoro-1-[3-hydroxy-4-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenyl]ethan-1-one;

1-(4-chloro-2,6-difluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-fluoro-6-methyl-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-nitrophenol;

2-{4-[(1-methylpiperidin-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

5-(cyclopropylethynyl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

5-ethynyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(prop-1-yn-1-yl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(prop-1-yn-1-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{1-[(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-{1-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-3-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{4-[3-(dimethylamino)piperidin-1-yl]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[4-(difluoromethyl)-2-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

5-(cyclopropyloxy)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(pyridin-3-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

1-(2-cyclopropyl-4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(1-methylpiperidin-2-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

1-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

1-[4-(difluoromethyl)-2-fluorophenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}thieno[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-azepan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-{4-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(azepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-(4-methoxy-2-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(3-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-3-methyl[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[3-(2,2-difluoroethyl)cyclobutyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

4-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

4-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine;

2-{1-[(4-methyl-1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(4-methyl-1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(1-methylazepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-{4-[(1,4-dimethyl-1,4-diazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-5,5-difluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidine-2-carboxylate;

3-methoxy-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzene-1,3-diol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3R)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxetan-3-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-(4-cyclopropyl-2-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-methylphenol;

3-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[2-(dimethylamino)-2-methylpropyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethyl)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-[4-(cyclohexylamino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-methyl-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-methylpiperidin-3-yl]-1-{2-[(propan-2-yl)oxy]-4-(trifluoromethyl)phenyl}pyrido[3,4-d]pyridazin-4-amine;

2-(4-{methyl[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(3-fluoropropyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[4-methoxy-2-(propan-2-yl)phenyl]-N-[(3S)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{methyl[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-methyl-2-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(4-{[(3R)-1-(1-^{2}H)cyclobutylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S,4R)-4-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1-methylpiperidin-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({[1-(2-hydroxyethyl)piperidin-4-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol;

3-fluoro-5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

5-ethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol;

2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3S)-oxan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

N-[(3R)-1-cyclobutylpiperidin-3-yl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)phenol;

2-(4-{[(3S,4R)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1r,3r)-3-hydroxy-3-methylcyclobutyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)-1-methylpiperidine-2-carboxylate;

1-[2-(difluoromethyl)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amin;e

1-[2-(difluoromethyl)-5-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine;

2-(8-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

N-[(3R)-azocan-3-yl]-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-methoxy-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-cyclopropyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(2-methyl-4-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(2-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(2-methyl-4-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

3-fluoro-5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol;

2-(4-{[(6S)-4-methyl-4-azaspiro[2.5]octan-6-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol;

2-(2-cyclopropyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

2-(2-cyclopropyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methoxyphenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-methoxy-2-(2-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-7-yl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

3-fluoro-5-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

(1S,3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)cyclohexan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(1R,3S)-3-methoxycyclohexyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-chloro-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

4-[4-bromo-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-oxan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

(1R,3S)-N^1-{1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}cyclohexane-1,3-diamine;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

4-[4-methoxy-2-(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

4-[2,4-bis(trifluoromethyl)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

1-(4-chloro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

(3R,5R)-5-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol;

8-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,2-d][1,2,4]triazin-5-amine;

(3R,5R)-5-{[1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino}-1-methylpiperidin-3-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(2S)-1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-piperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R)-piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

N-[(3R)-1-ethylpiperidin-3-yl]-1-[4-methoxy-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[4-methyl-2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,2-d][1,2,4]triazin-8-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methoxy-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)benzonitrile;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-(trifluoromethyl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxy-2-methylpropyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

4-[4-cyclopropyl-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-5-methyl-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethyl)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(oxan-4-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-(trifluoromethoxy)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(2R)-1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3S)-3-hydroxycyclopentyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1R,3R)-3-hydroxycyclopentyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-{4-[(3-hydroxy-3-methylcyclohexyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-(trifluoromethyl)phenol;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

2-[(3R)-3-({1-[4-methoxy-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

5-chloro-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3S)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3S)-oxolan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-methyl-1,2,3,6-tetrahydropyridin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2,3]triazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-oxan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[(3R)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]-2-methylpropan-2-ol;

1-[2-(difluoromethoxy)-4-methoxyphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1r,3r)-3-({1-[2-(difluoromethoxy)-4-methoxyphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-oxolan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[(3R)-3-({1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]-2-methylpropan-2-ol;

3,5-dimethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3S,4S)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(2,2,2-trifluoroethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3S,4R)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-6-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-6-fluoro-4-methylphenyl]-N-[(3R)-1-(oxolan-3-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(oxolan-3-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-[(3R)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

(2R)-1-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)propan-2-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-cyclopropyl-3-fluoro-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

3-fluoro-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methylphenol;

5-cyclopropyl-3-fluoro-2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-[($^{2}H_{3}$)methyloxy]-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

1-[4-bromo-2-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-chloro-2-(difluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[4-chloro-2-(difluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[4-cyclopropyl-2-(difluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

5-cyclopropyl-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

3-fluoro-5-[($^2H_3$)methyloxy]-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-[($^2H_3$)methyloxy]phenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluoro-5-methylphenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(oxan-4-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(oxolan-3-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-chloro-2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(1S,3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)cyclohexan-1-ol;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

2-(8-fluoro-4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-2-methylpropan-2-ol;

(1s,3s)-3-({1-[2,4-bis(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

N-[(3R)-1-methylpiperidin-3-yl]-1-[4-methyl-2-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[4-cyclopropyl-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-2-methylpropan-2-ol;

(1s,3s)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}-5-methylphenol;

5-cyclopropyl-3-fluoro-2-{4-[(2-hydroxy-2-methylpropyl)amino]pyrrolo[1,2-d][1,2,4]triazin-1-yl}phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(6-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-bromo-2-(7-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

4-[2-(benzyloxy)-4-bromophenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-bromo-2-(7-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-oxan-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(7-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-chloro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

3-fluoro-5-methoxy-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

5-bromo-2-(4-{[(3R)-1-(1-hydroxypropan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluoro-5-methoxyphenol;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-chloro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

3-methyl-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol;

5-chloro-2-(4-{[(3R)-oxolan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

5-ethyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-{4-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-(2-methoxy-2-methylpropyl)pyrrolo[1,2-d][1,2,4]triazin-4-amine;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

3-fluoro-5-methyl-2-(4-{[(3R)-1-(2,2,2-trifluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(1s,3s)-3-({1-[2,4-bis(difluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylcyclobutan-1-ol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R,5S)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-cyclopropyl-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol;

5-chloro-2-(4-{[(3S)-oxolan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-chloro-2-(4-{[(1R,3S)-3-methoxycyclohexyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol;

5-cyclopropyl-2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluorophenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethoxy)phenol;

4-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]-2-methylpyrazolo[1,5-d][1,2,4]triazin-7-amine;

5-cyclopropyl-2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-methoxyphenol;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{[(3S)-oxolan-3-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(trifluoromethyl)phenyl]-N-{[(3R)-oxolan-3-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-7-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoro-N-[(3R)-1-(propan-2-yl)piperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-(8-fluoro-4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-fluoro-4-{[(2S)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

2-(8-fluoro-4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

(3R,5R)-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

5-cyclopropyl-2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-3-fluoro-2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-cyclopropyl-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

(3R,5R)-5-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-8-fluoropyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-ethylpiperidin-3-ol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

(3R,5R)-1-ethyl-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-3-ol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-methyl-5-(trifluoromethyl)phenol;

3-fluoro-2-(7-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol;

5-chloro-3-fluoro-2-(4-{[(3R)-oxan-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-{[(2S)-oxolan-2-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-{[(2R)-oxolan-2-yl]methyl}pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

2-[(3R)-3-({1-[2,4-bis(difluoromethoxy)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol;

1-[2,4-bis(difluoromethoxy)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine;

5-(difluoromethoxy)-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-(difluoromethoxy)-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-(difluoromethoxy)-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-(difluoromethoxy)-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol;

5-chloro-3-fluoro-2-(4-{[(oxolan-2-yl)methyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol;

5-bromo-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(1s,3s)-3-hydroxy-3-methylcyclobutyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

5-ethoxy-3-fluoro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol;

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methoxypheno;l

2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)-5-methylphenol;

5-methoxy-2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol;

(R)-2-(4-((1-ethylpiperidin-3-yl)amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3,5-dimethylphenol;

(3S,5R)-5-((1-(2-fluoro-6-hydroxy-4-methylphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-methylpiperidin-3-ol;

(3S,5R)-1-ethyl-5-((1-(2-fluoro-6-hydroxy-4-methylphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)piperidin-3-ol;

(3S,5R)-5-((1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-methylpiperidin-3-ol; and

(3S,5R)-5-((1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl)amino)-1-ethylpiperidin-3-ol;

wherein a form of the compound may be selected from the group consisting of a pharmaceutically acceptable salt, hydrate, solvate, racemate, enantiomer, diastereomer,stereoisomer, and tautomer form thereof.

15. A compound or form thereof, selected from the group consisting of:

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(pyrrolidin-3-yl)amino]phthalazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol hydrochloride;

2-(8-methyl-4-{[(3R)-piperidin-3-yl]amino}-5,6,7,8-tetrahydrophthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(piperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol hydrochloride;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol diformate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(1-methylpiperidin-3-yl)methyl]phthalazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenol formate;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol formate;

2-(1-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol N-ethylethanamine;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol diformate;

(3S,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)-1-methylpiperidin-3-ol formate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)-5-(trifluoromethyl)phenol formate;

(3R,5R)-5-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-3-ol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}furo[2,3-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

5-methyl-2-(8-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-5-yl)phenol formate;

[(3R)-3-({4-[2-hydroxy-4-(trifluoromethyl)phenyl]phthalazin-1-yl}amino)piperidin-1-yl]acetic acid formate;

2-{1-[(piperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol hydrochloride;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(1-methylpyrrolidin-3-yl)phenol formate;

2-[1-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-4-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-pyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-1-methylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-{1-[(1-methylpiperidin-3-yl)methyl]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-amino-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]methanesulfonamide formate;

4-[2-(methylamino)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

N-[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(trifluoromethyl)phenyl]acetamide formate;

1-[2-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-(4-chloro-2-fluorophenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[4-chloro-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

1-[2-chloro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

4-[2-methoxy-4-(trifluoromethyl)phenyl]-1-methyl-N-[(3R)-1-methylpiperidin-3-yl]-1H-pyrazolo[3,4-d]pyridazin-7-amine formate;

2-(1-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}-1H-pyrazolo[3,4-d]pyridazin-4-yl)-5-(trifluoromethyl)phenol formate;

2-(1-methyl-8-{[(3R)-1-methylpiperidin-3-yl]amino}-1,2,3,4-tetrahydropyrido[2,3-d]pyridazin-5-yl)-5-(trifluoromethyl)phenol triformate;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile formate;

2-amino-3-chloro-6-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol formate;

4-(2,3-difluoro-4-methylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]phthalazin-1-amine formate;

5-methoxy-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

1-[2,4-bis(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-methoxy-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)benzamide formate;

5-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-8-amine formate;

8-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[2,3-d]pyridazin-5-amine formate;

2-{1-[(1-methylazepan-3-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-methylazepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(1-methyl-1H-pyrazol-4-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

[2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenyl]methanol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-(2,4,6-trimethylphenyl)pyrido[3,4-d]pyridazin-4-amine formate;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidin-1-yl]ethan-1-ol formate;

6-chloro-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

6-chloro-3-fluoro-2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[2,3-d]pyridazin-8-yl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

3-methyl-4-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzonitrile formate;

1-(4-chloro-2,6-dimethylphenyl)-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2,2,2-trifluoro-1-[3-hydroxy-4-(4-{[(3R)-piperidin-3-yl]amino}phthalazin-1-yl)phenyl]ethan-1-one formate;

5-(cyclopropylethynyl)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)phenol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}phthalazin-1-yl)-5-(prop-1-yn-1-yl)phenol formate;

N-[(3R)-1-methylpiperidin-3-yl]-1-[2-(prop-1-yn-1-yl)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-{1-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-4-yl}-5-(trifluoromethyl)phenol formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-piperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]pyrido[3,4-d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

5-(cyclopropyloxy)-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

2-[(3R)-3-({4-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-1-yl}amino)piperidin-1-yl]ethan-1-ol formate;

4-[2-(difluoromethoxy)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

4-[2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

4-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]-6,7-dihydro-5H-cyclopenta[d]pyridazin-1-amine formate;

1-[4-cyclopropyl-2-(difluoromethoxy)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

1-[4-cyclopropyl-2-(difluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

N-[(3R)-azepan-3-yl]-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-{4-[(1,4-oxazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-{4-[(azepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-(3-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}-3-methyl[1,2]oxazolo[4,5-d]pyridazin-7-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-azepan-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-{4-[(1-methylazepan-4-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

2-{4-[(1,4-dimethyl-1,4-diazepan-6-yl)amino]pyrido[3,4-d]pyridazin-1-yl}-5-(trifluoromethyl)phenol formate;

ethyl (2S,5R)-5-({1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-yl}amino)piperidine-2-carboxylate hydrochloride;

5-methyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)benzene-1,3-diol formate;

2-(4-{[(1R,3S)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(1R,3R)-3-hydroxycyclohexyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-methylphenol formate;

2-(4-{[2-(dimethylamino)-2-methylpropyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-methoxy-4-(trifluoromethyl)phenyl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(3S,5S)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-chloro-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

5-cyclopropyl-3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

3-fluoro-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

2-[4-({(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-(difluoromethyl)-4-methylphenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrido[3,4-d]pyridazin-4-amine formate;

2-(4-{[(1-methylpiperidin-4-yl)methyl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-[4-({[1-(2-hydroxyethyl)piperidin-4-yl]methyl}amino)pyrido[3,4-d]pyridazin-1-yl]-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-ethyl-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrido[3,4-d]pyridazin-1-yl)phenol formate;

N-{(3R)-1-[2-(difluoromethoxy)ethyl]piperidin-3-yl}-1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

2-[(3R)-3-({1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)piperidin-1-yl]ethan-1-ol formate;

2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

1-(4-chloro-2-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

5-chloro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

8-[2-methoxy-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,2-d][1,2,4]triazin-5-amine formate;

(3R,5R)-5-{[1-(4-cyclopropyl-2-fluoro-6-hydroxyphenyl)pyrrolo[1,2-d][1,2,4]triazin-4-yl]amino}-1-methylpiperidin-3-ol formate;

4-(4-bromo-2-methoxyphenyl)-N-[(3R)-piperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-(4-{[(3R)-oxan-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(5-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,2-d][1,2,4]triazin-8-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R,5R)-5-fluoropiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

4-[4-cyclopropyl-2-(trifluoromethoxy)phenyl]-2-methyl-N-[(3R)-1-methylpiperidin-3-yl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-methyl-N-[(3R)-1-methylpiperidin-3-yl]-4-[2-(trifluoromethoxy)phenyl]pyrazolo[1,5-d][1,2,4]triazin-7-amine formate;

2-(4-{[(2R)-2-hydroxypropyl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

2-(8-fluoro-4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol hydrochloride;

5-chloro-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

5-chloro-3-fluoro-2-(2-methyl-7-{[(3R)-1-methylpiperidin-3-yl]amino}pyrazolo[1,5-d][1,2,4]triazin-4-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3S)-oxolan-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

2-(4-{[(3R)-1-methyl-1,2,3,6-tetrahydropyridin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(7-{[(3R)-1-methylpiperidin-3-yl]amino}[1,2,3]triazolo[1,5-d][1,2,4]triazin-4-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3S,4S)-4-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(4-{[(3R)-1-(propan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

1-[2-(difluoromethoxy)-6-fluoro-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

1-[4-chloro-2-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]pyrrolo[1,2-d][1,2,4]triazin-4-amine formate;

5-cyclopropyl-2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluorophenol formate;

2-(4-{[(3R)-1-(2,2-difluoroethyl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-3-fluoro-5-methylphenol formate;

2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(6-methyl-4-{[(3R)-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

5-bromo-2-(4-{[(3R)-1-(1-hydroxypropan-2-yl)piperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

5-cyclopropyl-2-(7-{[(3R)-1-ethylpiperidin-3-yl]amino}-2-methylpyrazolo[1,5-d][1,2,4]triazin-4-yl)-3-fluorophenol formate;

5-chloro-2-(4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

5-ethyl-3-fluoro-2-(4-{[(3R)-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-ethylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate;

2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluoro-5-methylphenol formate;

5-cyclopropyl-2-[4-({[(2S)-1-ethylpyrrolidin-2-yl]methyl}amino)pyrrolo[1,2-d][1,2,4]triazin-1-yl]-3-fluorophenol formate;

2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

2-(8-fluoro-4-{[(3R,5R)-5-fluoro-1-methylpiperidin-3-yl]amino}pyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethyl)phenol formate;

(3R,5R)-5-({8-fluoro-1-[2-hydroxy-4-(trifluoromethyl)phenyl]pyrrolo[1,2-d][1,2,4]triazin-4-yl}amino)-1-methylpiperidin-3-ol formate;

2-(4-{[(3R,5R)-1-ethyl-5-fluoropiperidin-3-yl]amino}-8-fluoropyrrolo[1,2-d][1,2,4]triazin-1-yl)-5-(trifluoromethoxy)phenol formate;

5-bromo-2-(4-{[(3R)-1-(2-hydroxyethyl)piperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

1-[2-(difluoromethoxy)-4-(trifluoromethyl)phenyl]-N-[(3R)-1-methylpiperidin-3-yl]imidazo[1,5-d][1,2,4]triazin-4-amine formate; and

5-bromo-2-(4-{[(3R)-1-ethylpiperidin-3-yl]amino}imidazo[1,5-d][1,2,4]triazin-1-yl)phenol formate;

wherein a form of the compound may be selected from the group consisting of a hydrate, solvate, racemate, enantiomer, diastereomer, stereoisomer, and tautomer form thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

17. A method for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound according to of any one of claims 1 to 15.

18. A method of treating or ameliorating a disease modulated by NLRP3 according to claim 17 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease, VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, e.g. Duchenne Muscular Dystrophy (DMD), Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

19. The method of any one of claims 17 to 18, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

20. A compound according to any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, for use in treating or ameliorating a disease modulated by NLRP3 selected from Alzheimer disease, Frontotemporal dementia (FTD), Huntington's disease, Parkinson's disease, Perioperative neurocognitive disorders, Post–cardiac arrest cognitive impairment, Poststroke cognitive impairment, Sepsis, Sepsis associated encephalopathy, Subarachnoid hemorrhage, Macular Degeneration, Retinal neovascularization, Uveitis, Colitis, Endothelial dysfunction, Gout, Pseudogout, Graft-versus-host-disease (GvHD), Systemic lupus erythematosus–lupus nephritis, Cryopyrin-associated periodic syndromes (CAPS), Cystic fibrosis, Sickle-cell disease,

VCP-associated disease, Liver fibrosis, Nonalcoholic fatty liver disease (NASH), muscle atrophy, inherited and acquired myopathies, Hyperalgesia, Multiple sclerosis–associated neuropathic pain, Acute Kidney Injury, Chronic crystal nephropathy, Chronic Kidney Disease, asthma and allergic airway inflammation Diabetes-associated atherosclerosis, Diabetic encephalopathy, Diabetic kidney disease, Islet transplantation rejection, Obesity-associated renal disease, Oxalate-induced nephropathy, Renal fibrosis, Renal hypertension, Type I diabetes, Type II diabetes, Psoriasis, Hidradenitis suppurativa, Atherosclerosis and Cytokine Release Syndrome (CRS).

21. Use of a compound according to any one of claims 1 to 15, wherein the effective amount of the compound is in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day.

22. Use of a compound according to any one of claims 1 to 15 in the preparation of a pharmaceutical composition for treating or ameliorating a disease modulated by NLRP3 in a subject in need thereof comprising, administering to the subject an effective amount of the compound or a form thereof in admixture with one or more of the pharmaceutically acceptable excipients.