

BICYCLIC COMPOUNDS FOR KETOHEXOKINASE INHIBITION**FIELD OF THE DISCLOSURE**

[0001] This disclosure relates generally to novel ketohexokinase (KHK) inhibitor compounds, pharmaceutical compositions thereof, and the use of these compounds for the treatment of conditions such as non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatohepatitis (MASH), metabolic dysfunction-associated steatotic liver disease (MASLD), non-alcoholic steatohepatitis (NASH), hypertriglyceridemia, hypercholesterolemia, type 2 diabetes mellitus (T2D), diabetic kidney disease (DKD), alcoholic steatohepatitis (ASH), addictive craving including sugar or alcohol craving or alcohol use disorder, neurodegenerative diseases such as Parkinson's Disease or Alzheimer's Disease, hyperuricemia, gout, or cancer.

BACKGROUND

[0002] KHK (also called ketohexokinase or fructokinase) catalyzes the first step in fructose metabolism, phosphorylating fructose to fructose-1-phosphate (F1P) and depleting intracellular ATP. There is no negative feedback mechanism by which F1P inhibits KHK metabolism of fructose, therefore accumulation of F1P is directly related to the amount of fructose either (1) transported into the cell via the GLUT transporters or (2) formed intracellularly from glucose via the polyol pathway, and metabolized via KHK. The accumulation of F1P and depletion of ATP cause deleterious consequences in cells and tissue, including oxidative stress, osmolar stress, endothelial dysfunction, and metabolic dysregulation. Responses to these insults include lipogenesis, hyperuricemia and gluconeogenesis, which drive metabolic diseases including metabolic syndrome and its sequelae.

[0003] Two isoforms of KHK exist: KHK-A, which is ubiquitously expressed but has a lower affinity for fructose, and KHK-C, which is preferentially expressed in liver, kidney, brain, and intestine with a much higher affinity for fructose. While KHK-C drives the majority of physiological flux from fructose to F1P, KHK-A may compensate for downregulation, inhibition, or deletion of KHK-C, particularly as intracellular fructose concentrations rise. Humans with genetic polymorphisms in *KHK* have the benign phenotype Essential Fructosuria and do not accumulate F1P, whereas the more serious condition Hereditary Fructose Intolerance is caused by a polymorphism in the *ALDOB* gene encoding aldolase B, which catalyzes the second step in fructose metabolism, leading to deleterious accumulation of F1P and increased oxidative stress caused by depletion of the intracellular adenine nucleotide pool.

[0004] Increased consumption of fructose and fructose-containing polysaccharides like sucrose and high-fructose corn syrup is associated with the rise in metabolic disorders including obesity, insulin resistance, type 2 diabetes, dyslipidemia, metabolic liver diseases including NASH and other liver diseases associated with increased hepatocyte stress including alpha-1 antitrypsin deficiency and hemochromatosis. Targeting this first, rate-limiting step of fructose metabolism, i.e., phosphorylation by KHK, has been suggested to be a promising therapeutic strategy for these metabolic disorders as well as other diseases driven by fructose metabolism: cancers, neurodegenerative disorders including Parkinson's disease and Alzheimer's disease, addictive cravings for sugar and alcohol, hyperuricemia, and other complications of insulin resistance including diabetic retinopathy and diabetic kidney disease.

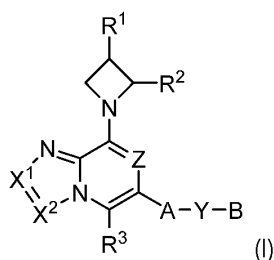
[0005] Attempts to inhibit KHK have thus far stalled in preclinical or clinical development, with only modest inhibition of fructose uptake and metabolism demonstrated by the furthest-developed compound, PF-06835919, in phase 1 and phase 2 clinical studies. While this molecule demonstrated potent inhibition of the isolated KHK-C enzyme, its potency was reduced approximately 10-fold in a cell-based assay of KHK activity, translating to the need for twice-daily 300mg doses in the phase 2 clinical study. Even with these high doses, only modest effects on liver fat and markers of liver injury were observed. As a carboxylic acid, PF-06835919 is a substrate of organic anion transporter protein, leading to increased accumulation in liver relative to other tissues and organs. While KHK-C is preferentially expressed in liver, it is also highly expressed in kidney, intestine and some brain centers, other sites of fructose metabolism to F1P, which may drive metabolic dysregulation, endothelial dysfunction, metabolic disease or craving disorders. Further, PF-06835919 is a KHK-C-biased inhibitor, with much weaker inhibition of KHK-A. PF-06835919 is disclosed in US 2017/0183328 A1. See also, J. Med. Chem. 2020, 63, 13546-13560. In addition, U.S. patent no. 11,124,500 discloses certain disubstituted pyrazole KHK inhibitor compounds. Also, Durham et. al. J. Med Chem. 2023, 66, 15960-15976 *"Identification of LY3522348: A Highly Selective and Orally Efficacious Ketohexokinase Inhibitor"*, discloses ketohexokinase inhibitors. While KHK-C drives fructose metabolism in several tissues at physiological fructose concentrations, as fructose concentrations rise (due to diet, metabolic disease, or inhibition of KHK-C), the contribution of KHK-A metabolism of fructose to F1P becomes more substantial.

[0006] Therefore, there is significant need to develop a KHK inhibitor that is potent both in enzyme assays and in cell-based assays; provides balanced inhibition of KHK-C and KHK-A to minimize escape flux to F1P through KHK-A or compensation by KHK-A; and is systemically distributed to inhibit KHK-C and KHK-A in not just liver, but also kidney, intestine, and all other tissues.

SUMMARY

[0007] The present disclosure generally relates to methods of inhibiting ketohexokinase (KHK), to methods of treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol), and to compounds and compositions that can be employed for such methods.

[0008] The disclosure provides compounds of Formula (I), and pharmaceutically acceptable salts thereof:



wherein

each of X¹ and X² is independently N or CR⁴; Z is N or CR⁵; R¹ is H or OH; R² is C₁₋₆alkyl or C₁₋₆haloalkyl; R³ is H, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₁₋₆alkoxy; R⁴ is H, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₃₋₁₀ cycloalkyl; R⁵ is H, halo, C₁₋₆alkyl, or C₁₋

₆haloalkyl; Y is a bond or C₁₋₆alkylene-C(O); A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶; B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R⁶; each R⁶ independently is OH, halo, CN, -N(R^a)(R^b), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, or C₁₋₆alkoxy; and R^a and R^b are independently H or C₁₋₃alkyl.

[0009] Further provided are methods of administering to a biological sample or patient a safe and effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0010] Also provided herein are methods of inhibiting ketohexokinase (KHK) in a biological sample or in a patient (e.g., in a cell) by administering to said biological sample or patient an effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0011] Further provided are methods of treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol), comprising administering to said subject an effective amount of a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A.

[0012] Also provided are pharmaceutical compositions comprising a compound as disclosed herein, e.g., as represented by Formula (I) or a compound of Table A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, adjuvant or vehicle.

[0013] Also provided are uses of a compound described herein for inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol).

[0014] Further provided herein are uses of a compound described herein for the manufacture of a medicament for inhibiting ketohexokinase (KHK), and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including via excessive consumption of fructose and/or alcohol).

DETAILED DESCRIPTION

[0015] Provided herein are compounds, and their use in inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol). Also provided are uses of the compounds described herein, or pharmaceutically acceptable salts thereof, or pharmaceutically acceptable compositions comprising such a compound or a pharmaceutically acceptable salt thereof, for inhibiting ketohexokinase (KHK), e.g., in a cell, and for treating or preventing diseases or disorders in a subject (e.g., wherein the diseases or disorders are associated with KHK dysregulation).

[0016] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, cis-trans, conformational, and rotational) forms of the structure. For example, the R and S

configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers are included in this disclosure, unless only one of the isomers is specifically indicated. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, cis/trans, conformational, and rotational mixtures of the present compounds are within the scope of the disclosure. In some cases, the compounds disclosed herein are stereoisomers. "Stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds disclosed herein can exist as a single stereoisomer, or as a mixture of stereoisomers. Stereochemistry of the compounds shown herein indicate a relative stereochemistry, not absolute, unless discussed otherwise. As indicated herein, a single stereoisomer, diastereomer, or enantiomer refers to a compound that is at least more than 50% of the indicated stereoisomer, diastereomer, or enantiomer, and in some cases, at least 90% or 95% of the indicated stereoisomer, diastereomer, or enantiomer.

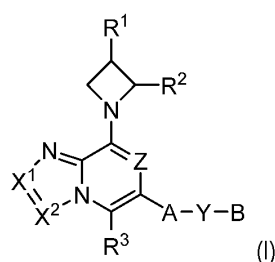
[0017] Unless otherwise indicated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0018] Additionally, unless otherwise indicated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays. Such compounds, especially deuterium analogs, can also be therapeutically useful.

[0019] The compounds of the disclosure are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

Compounds

[0020] Provided herein are compounds of Formula (I), and pharmaceutically acceptable salts thereof:



wherein

each of X^1 and X^2 is independently N or CR^4 ;

Z is N or CR^5 ;

R^1 is H or OH;

R^2 is C_{1-6} alkyl or C_{1-6} haloalkyl;

R^3 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy;

R^4 is H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-10} cycloalkyl;

R⁵ is H, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl;

Y is a bond or C₁₋₆alkylene-C(O);

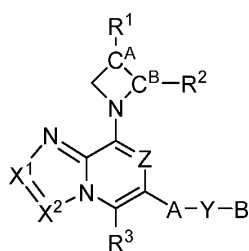
A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶;

B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R⁶;

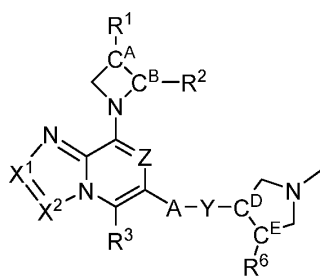
each R⁶ independently is OH, halo, CN, -N(R^a)(R^b), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, or C₁₋₆alkoxy; and

R^a and R^b are independently H or C₁₋₃alkyl. In some cases, each of X¹ and X² is N or CR⁴; Z is N or CR⁵; R¹ is H or OH; R² is C₁₋₆alkyl or C₁₋₆haloalkyl; R³ is H, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₁₋₆alkoxy; R⁴ is H, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₃₋₁₀ cycloalkyl; R⁵ is H, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl; Y is a bond or C₁₋₆alkylene-C(O); A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶; B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R⁶; each R⁶ independently is OH, halo, CN, -N(R^a)(R^b), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, or C₁₋₆alkoxy; and R^a and R^b are independently H or C₁₋₃alkyl.

[0021] In some cases, the compound of Formula I has the structure of Formula II:



Formula II, wherein C^A and C^B each represent a carbon stereocenter. In some cases, the compound of Formula I has the structure of structure of Formula III:



Formula III wherein C^A, C^B, C^D and C^E each represent a carbon stereocenter. In some cases, C^A is a carbon in the R configuration and C^B is a carbon in the R configuration. In some cases, C^A is a carbon in the R configuration and C^B is a carbon in the S configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, and C^D and C^E are carbons in the R configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, and C^D and C^E are carbons in the S configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, C^D is a carbon in the R configuration, and C^E is a carbon in the S configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, and C^D and C^E are carbons in the R configuration.

In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, and C^D and C^E are carbons in the S configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the R configuration, and C^E is a carbon in the S configuration. In some cases, C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the S configuration, and C^E is a carbon in the R configuration.

[0022] In some cases, one of X¹ and X² is N and the other is CR⁴. In some cases, X¹ is N and X² is CR⁴. In some cases, X¹ is CR⁴ and X² is N. In some cases, R⁴ is H, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl. In some cases, R⁴ is H, halo, or C₁₋₆haloalkyl. In some cases, R⁴ is H, fluoro, or CF₃. In some cases, R⁴ is H. In some cases, R⁴ is halo. In some cases, R⁴ is fluoro. In some cases, R⁴ is C₁₋₆alkyl. In some cases, R⁴ is methyl. In some cases, R⁴ is C₁₋₆haloalkyl. In some cases, R⁴ is CHF₂ or CF₃. In some cases, R⁴ is CHF₂. In some cases, R⁴ is CF₃. In some cases, R⁴ is C₃₋₁₀cycloalkyl. In some cases, R⁴ is cyclopropyl.

[0023] In some cases, Z is N. In some cases, Z is CR⁵. In some cases, R⁵ is H. In some cases, R⁵ is halo. In some cases, R⁵ is C₁₋₆alkyl. In some cases, R⁵ is C₁₋₆haloalkyl.

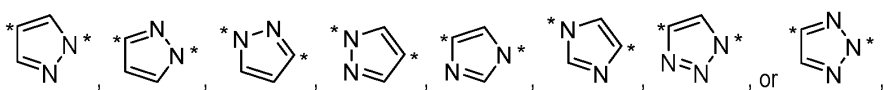
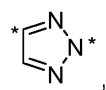
[0024] In some cases, R¹ is H. In some cases, R¹ is OH.

[0025] In some cases, R² is C₁₋₆alkyl. In some cases, R² is methyl. In some cases, R² is C₁₋₆haloalkyl. In some cases, R² is C₁haloalkyl. In some cases, R² is CHF₂ or CF₃. In some cases, R² is CHF₂. In some cases, R² is CF₃.

[0026] In some cases, R³ is H or C₁₋₆alkyl. In some cases, R³ is H or methyl. In some cases, R³ is H. In some cases, R³ is C₁₋₆alkyl. In some cases, R³ is methyl. In some cases, R³ is C₁₋₆haloalkyl. In some cases, R³ is C₁haloalkyl. In some cases, R³ is CHF₂ or CF₃. In some cases, R³ is CHF₂. In some cases, R³ is CF₃. In some cases, R³ is C₁₋₆alkoxy. In some cases, R³ is methoxy.

[0027] In some cases, Y is a bond. In some cases, Y is C₁₋₆alkylene-C(O). In some cases, Y is C₁alkylene-C(O).

[0028] In some cases, A is 5-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶. In some cases, A is 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶. In some cases, A has 1 ring nitrogen atom. In some cases, A has 2 ring nitrogen atoms. In some cases, A has 3 ring nitrogen atoms. In some cases, A is unsubstituted. In some cases, A is substituted independently with 1 or 2 R⁶. In some cases, A is substituted independently with 1 R⁶. In some cases, A is substituted independently with 2 R⁶. In some cases, A is pyrazolyl, imidazolyl, or triazolyl optionally substituted with 1 or 2 R⁶. In some cases, A is pyrazolyl optionally substituted with 1 or 2 R⁶. In some cases, A is imidazolyl optionally substituted with 1 or 2 R⁶. In some cases, A is triazolyl optionally substituted with 1 or 2 R⁶. In

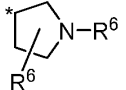
some cases, A is , or ,

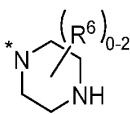
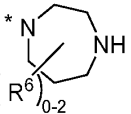
wherein each * indicates a point of attachment to the rest of the compound, and A is optionally substituted with 1 or 2

R⁶. In some cases, A is . In some cases, A is . In some cases, A is . In some cases, A

is . In some cases, A is . In some cases, A is . In some cases, A is . In some cases, A is .

[0029] In some cases, B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R^6 . In some cases, B is a 4- or 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R^6 . In some cases, B is 4-membered heterocycloalkyl having 1 nitrogen atom, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R^6 . In some cases, B is 5-membered heterocycloalkyl having 1 ring nitrogen atom, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R^6 . In some cases, B is 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R^6 . In some cases, B has 1 ring nitrogen atom. In some cases, B has 2 ring nitrogen atoms. In some cases, B is unsubstituted. In some cases, B is substituted independently with one or two R^6 . In some cases, B is substituted independently with one R^6 . In some cases, B is substituted independently with two R^6 . In some cases, B is substituted independently with 2 R^6 . In some cases, B is azetidiny, pyrrolidinyl,

piperazinyl, or diazepinyl optionally substituted with 1 or 2 R^6 . In some cases, B is , ,

, or , wherein * indicates a point of attachment to the rest of the compound. In some cases, B is azetidiny or piperazinyl optionally substituted with 1 or 2 R^6 . In some cases, B is azetidiny. In some cases,

B is piperazinyl. In some cases, B is  or , wherein * indicates a point of attachment to the rest of the

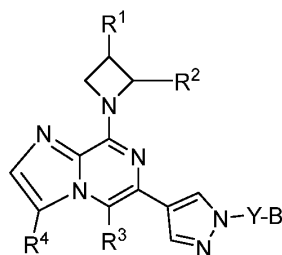
compound. In some cases, B is . In some cases, B is .

[0030] In some cases, at least one R^6 is OH. In some cases, each R^6 is OH. In some cases, at least one R^6 is halo. In some cases, each R^6 is halo. In some cases, at least one R^6 is CN. In some cases, each R^6 is CN. In some cases, at least one R^6 is $-N(R^a)(R^b)$. In some cases, each R^6 is $-N(R^a)(R^b)$. In some cases, at least one of R^a and R^b is H. In some cases, each of R^a and R^b is H. In some cases, at least one of R^a and R^b is C_{1-3} alkyl. In some cases, each of R^a and R^b is C_{1-3} alkyl. In some cases, at least one of R^a and R^b is methyl. In some cases, each of R^a and R^b is methyl. In some cases, at least one R^6 is C_{1-6} alkyl. In some cases, each R^6 is C_{1-6} alkyl. In some cases, at least one R^6 is methyl. In some cases, each R^6 is methyl. In some cases, at least one R^6 is C_{1-6} haloalkyl. In some cases, each R^6 is C_{1-6} haloalkyl. In some cases, at least one R^6 is C_{1-6} hydroxyalkyl. In some cases, each R^6 is C_{1-6} hydroxyalkyl. In some cases, at least one R^6 is C_{1-6} alkoxy. In some cases, each R^6 is C_{1-6} alkoxy.

[0031] In some cases, Z is N, X¹ is CR⁴ and R⁴ is H, chloro, fluoro or C₁₋₂alkyl, R² is

trifluoromethyl or C₁₋₂alkyl, R³ is H or C₁₋₂alkyl, A is , Y is a bond wherein * indicates a point of attachment to

the rest of the compound or C₁alkylene-C(O), B is R⁶ or , and R⁶ is C₁₋₂alkyl. In some cases, structure of Formula (IV):



(IV), wherein R⁴ is H, chloro, fluoro or C₁₋₂alkyl, R² is trifluoromethyl or C₁₋₂alkyl, R³ is H

or C₁₋₂alkyl, Y is a bond or C₁alkylene-C(O), B is R⁶ or , and R⁶ is C₁₋₂alkyl.

[0032] As used herein, the term "alkyl" or "alkylene" means a saturated straight or branched chain hydrocarbon. The term C_n means the alkyl group has "n" carbon atoms. For example, C₄alkyl refers to an alkyl group that has 4 carbon atoms. C₁₋₆alkyl refers to an alkyl group having a number of carbon atoms encompassing the entire range (i.e., 1 to 6 carbon atoms), as well as all subgroups (e.g., 1-6, 2-6, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3, 1-2, 2-2, 1-1, 2-1, 3, 4, 5, and 6 carbon atoms). Specific examples include, but are not limited to, methyl, ethyl, isopropyl, n-propyl, sec-butyl, and t-butyl.

[0033] As used herein, the terms "halogen" and "halo" mean F, Cl, Br, or I.

[0034] As used herein, the term "haloalkyl" refers to an alkyl group substituted with one or more halogen substituents. For example, C₁-C₆haloalkyl refers to a C₁-C₆ alkyl group substituted with one or more halogen atoms, e.g., 1, 2, 3, 4, 5, or 6 halogen atoms. Non-limiting examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, and trichloromethyl groups.

[0035] As used herein, the term "hydroxyalkyl" refers to an alkyl group substituted with one or more hydroxy (OH) substituents. For example, C₁-C₆hydroxyalkyl refers to a C₁-C₆ alkyl group substituted with one or more hydroxy groups, e.g., 1, 2, 3, 4, 5, or 6 hydroxy groups. Non-limiting examples of hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, or hydroxypropyl groups.

[0036] The term "alkoxy" used herein refers to an -O-alkyl group.

[0037] The term "heterocycloalkyl" as used herein refers to a non-aromatic monocyclic, fused, spiro or bridged ring system which can be saturated or contain one or more units of unsaturation, having four to six ring atoms in which one or two ring atoms is a nitrogen atom. In some embodiments, the heterocycloalkyl comprises 4 or 8 ring members. In

some embodiments, the heterocycle comprises 4 ring members. In some embodiments, the heterocycloalkyl comprises 6 ring members.

[0038] Examples of heterocycloalkyls include, but are not limited to, oxetanyl, azetidiny, thietanyl, piperidiny, piperazinyl, pyrrolidiny, pyrazolidiny, imidazolidiny, oxazolidiny, isoxazolidiny, thiazolidiny, isothiazolidiny, tetrahydrofuranyl, tetrahydrothiophenyl, morpholino (including, for example, 3-morpholino, 4-morpholino), 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidiny, 2-pyrrolidiny, 3-pyrrolidiny, pyrrolidin-2-one, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidiny, 2-piperidiny, 3-piperidiny, 1-pyrazoliny, 3-pyrazoliny, 4-pyrazoliny, 5-pyrazoliny, 1-piperidiny, 2-piperidiny, 3-piperidiny, 4-piperidiny, 2-thiazolidiny, 3-thiazolidiny, 4-thiazolidiny, 1-imidazolidiny, 2-imidazolidiny, 4-imidazolidiny, 5-imidazolidiny, dihydrofuranyl, 1,3 dioxolany, 1,4-dioxany, 1,3-oxathiol, oxathianyl, 1,3-dithianyl, 1,4-oxathiolany, 1,4-oxathianyl, 1,4-dithianyl, thiomorpholinyl, tetrahydropyrany, dihydropyrany, diazepenyl, and 1,3-dihydro-imidazol-2-onyl. A heterocycloalkyl ring is unsubstituted or substituted as described herein.

[0039] The term "heteroaryl" used herein refers to a heterocycle that is aromatic, having five or six members. Heteroaryl groups have one to three ring (e.g., 1 to 3, 1 or 2, 1, 2, or 3) ring nitrogen atoms. Examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, triazolyl (such as 1,2,3-triazolyl or 1,2,4-triazolyl), tetrazolyl, imidazolyl, and triazinyl (such as 1,2,3-triazinyl, 1,2,4-triazinyl, or 1,3,5-triazinyl). A heteroaryl ring is unsubstituted or substituted as described herein.

[0040] As described herein, compounds of the disclosure may optionally be substituted with one or more substituents, such as illustrated generally, or as exemplified by particular classes, subclasses, and species of the disclosure. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position.

[0041] Specific compounds contemplated include compounds in the following Tables. Compounds showing particular stereocenters indicate at least a relative stereoisomerism. Compounds having a chiral center without indication of a particular stereoisomerism indicate a mixture of stereocenters at that chiral center.

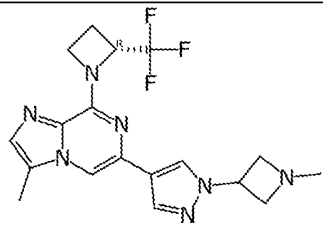
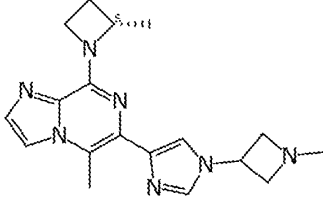
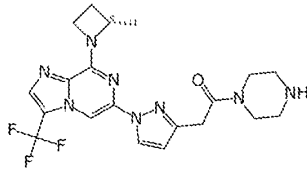
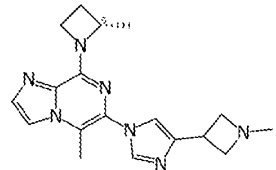
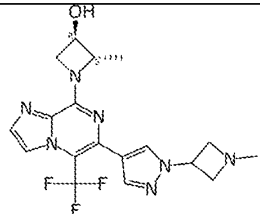
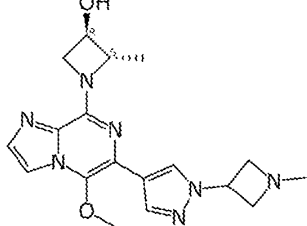
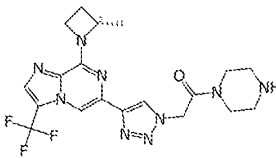
[0042] The compound can be a compound as listed in Table A, or a pharmaceutically acceptable salt thereof. The compounds in Table A were prepared according to methods described in the Examples section and other methods known to those skilled in the art. Compound names were generated by CDD Vault (project database) according to IUPAC nomenclature.

TABLE A

Compound No.	IUPAC Name	Structure
A1	2-(4-{7-[(S)-2-methyl-1-azetidiny]-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A2	(2S,3R)-2-methyl-1-{5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3,3a,6-tetraaza-7-indenyl}-3-azetidinol	
A3	7-[(S)-2-methyl-1-azetidiny]-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A4	7-[(S)-2-methyl-1-azetidiny]-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-3-(trifluoromethyl)-1,3a,6-triazaindene	
A5	(2S,3R)-2-methyl-1-{4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-3-azetidinol	
A6	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A7	(2S,3R)-2-methyl-1-{5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-3-azetidinol	

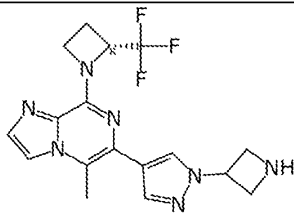
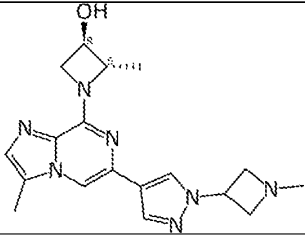
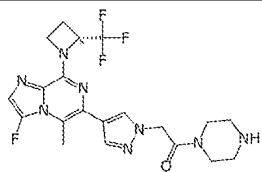
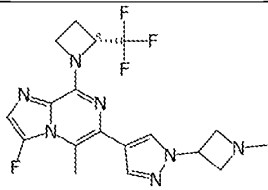
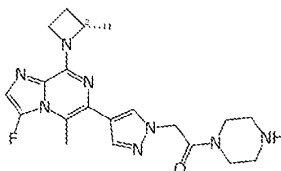
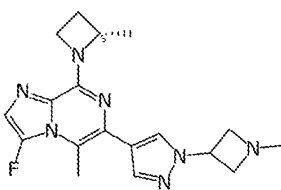
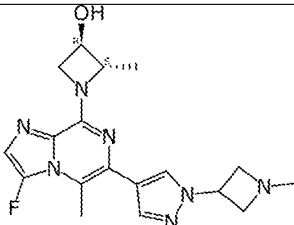
Compound No.	IUPAC Name	Structure
A8	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A9	7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A10	2-(4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A11	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A12	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A13	7-[(S)-2-methyl-1-azetidiny]-3-fluoro-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	

Compound No.	IUPAC Name	Structure
A14	(2S,3R)-1-{3-fluoro-5-[1-(1-methyl-3-azetidiny)]-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A15	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A16	4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-4-methyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A17	5-{1-[(R)-1-methyl-3-pyrrolidiny]-4-pyrazolyl}-7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triazaindene	
A18	(2S,3R)-1-{3-chloro-5-[1-(1-methyl-3-azetidiny)]-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A19	7-[(S)-2-methyl-1-azetidiny]-3-(difluoromethyl)-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A20	7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3,3a,6-tetraazaindene	

Compound No.	IUPAC Name	Structure
A21	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triazaindene	
A22	7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-imidazolyl]-1,3a,6-triazaindene	
A23	2-(1-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-3-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A24	7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[4-(1-methyl-3-azetidiny)-1-imidazolyl]-1,3a,6-triazaindene	
A25	(2S,3R)-2-methyl-1-{5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-4-(trifluoromethyl)-1,3a,6-triaza-7-indenyl}-3-azetidinol	
A26	(2S,3R)-1-{4-methoxy-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A27	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1H-1,2,3-triazol-1-yl)-1-(1-piperazinyl)-1-ethanone	

Compound No.	IUPAC Name	Structure
A28	((2S,3R)-2-methyl-1-{4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-3-(trifluoromethyl)-1,3a,6-triaza-7-indenyl}-3-azetidinol	
A29	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A30	2-(4-{7-[(S)-2-methyl-1-azetidiny]-4-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A31	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(2,2-dimethyl-1-piperazinyl)-1-ethanone	
A32	7-[(S)-2-methyl-1-azetidiny]-3-isopropyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A33	(3R,4R)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	

Compound No.	IUPAC Name	Structure
A34	(3S,4S)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A35	5-{1-[(3R,4S)-4-methoxy-1-methyl-3-pyrrolidinyl]-4-pyrazolyl}-7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triazaindene	
A36	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-4-(trifluoromethyl)-1,3,3a,6-tetraazaindene	
A37	4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3,4-dimethyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A38	4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A39	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	

Compound No.	IUPAC Name	Structure
A40	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-5-[1-(3-azetidiny)-4-pyrazoly]-4-methyl-1,3a,6-triazaindene	
A41	(2S,3R)-2-methyl-1-{3-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triaza-7-indenyl}-3-azetidinol	
A42	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A43	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triazaindene	
A44	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-fluoro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A45	7-[(S)-2-methyl-1-azetidiny]-3-fluoro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triazaindene	
A46	(2S,3R)-1-{3-fluoro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	

Compound No.	IUPAC Name	Structure
A47	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(4-methyl-1-piperazinyl)-1-ethanone	
A48	4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A49	7-[(S)-2-methyl-1-azetidiny]-3-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A50	2-(3-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A51	7-[(S)-2-methyl-1-azetidiny]-3-chloro-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A52	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-5-{1-[(S)-1-methyl-3-pyrrolidiny]-4-pyrazolyl}-4-methyl-1,3a,6-triazaindene	
A53	(2S,3R)-2-methyl-1-{4-methyl-5-[1-(1-methyl-3-azetidiny)-3-pyrazolyl]-1,3a,6-triaza-7-indenyl}-3-azetidinol	

Compound No.	IUPAC Name	Structure
A54	7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-3-pyrazolyl]-1,3a,6-triazaindene	
A55	7-[(S)-2-methyl-1-azetidiny]-3-fluoro-5-[1-(1-methyl-3-azetidiny)-3-pyrazolyl]-1,3a,6-triazaindene	
A56	(2S,3R)-1-{3-fluoro-5-[1-(1-methyl-3-azetidiny)-3-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A57	4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A58	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A59	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A60	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

Compound No.	IUPAC Name	Structure
A61	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A62	(2S,3R)-1-{3-chloro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A63	7-[(S)-2-methyl-1-azetidiny]-3,4-dimethyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A64	(2S,3R)-1-{3,4-dimethyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A65	7-[(S)-2-methyl-1-azetidiny]-3-chloro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A66	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3,4-dimethyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A67	4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	

Compound No.	IUPAC Name	Structure
A68	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3,4-dimethyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triazaindene	
A69	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazoly)-1-(1-piperazinyl)-1-ethanone	
A70	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazoly]-1,3a,6-triazaindene	
A71	4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A72	4-{7-[(S)-2-methyl-1-azetidiny]-3,4-dimethyl-1,3a,6-triaza-5-indenyl}-2-(1-methyl-3-azetidiny)-2H-1,2,3-triazole	
A73	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazoly)-1-(4-methyl-1-piperazinyl)-1-ethanone	
A74	4-{7-[(S)-2-methyl-1-azetidiny]-3,4-dimethyl-1,3a,6-triaza-5-indenyl}-1-(1-methyl-3-azetidiny)-1H-1,2,3-triazole	

Compound No.	IUPAC Name	Structure
A75	(2S,3R)-1-{3-isopropyl-5-[1-(1-methyl-3-azetidynyl)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A76	(2S,3R)-1-{5-[1-(3-azetidynyl)-4-pyrazolyl]-3-chloro-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A77	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidynyl]-3-(difluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A78	2-(4-{7-[(S)-2-methyl-1-azetidynyl]-3-(difluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A79	2-(4-{7-[(S)-2-methyl-1-azetidynyl]-3-(trifluoromethyl)-1,2,3a,6-tetraaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A80	7-[(R)-2-(trifluoromethyl)-1-azetidynyl]-3-(difluoromethyl)-4-methyl-5-[1-(1-methyl-3-azetidynyl)-4-pyrazolyl]-1,3a,6-triazaindene	
A81	(2S,3R)-1-{3-(difluoromethyl)-4-methyl-5-[1-(1-methyl-3-azetidynyl)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	

Compound No.	IUPAC Name	Structure
A82	(2S,3R)-1-{3-(difluoromethyl)-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A83	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-(difluoromethyl)-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A84	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A85	2-(4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-1,3,3a,6-tetraaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A86	(2S,3R)-2-methyl-1-{4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3,3a,6-tetraaza-7-indenyl}-3-azetidinol	
A87	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-5-[1-(3-azetidiny)-4-methyl-1,3,3a,6-tetraazaindene	
A88	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3,3a,6-tetraaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	

Compound No.	IUPAC Name	Structure
A89	7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3,3a,6-tetraazaindene	
A90	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3,4-dimethyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A91	(2S,3R)-2-methyl-1-{5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-3-(trifluoromethyl)-1,2,3a,6-tetraaza-7-indenyl}-3-azetidinol	
A92	7-[(S)-2-methyl-1-azetidiny]-3-cyclopropyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	
A93	(2S,3R)-1-{3-cyclopropyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol	
A94	2-(4-{7-[(S)-2-methyl-1-azetidiny]-4-methoxy-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperazinyl)-1-ethanone	
A95	7-[(S)-2-methyl-1-azetidiny]-4-methoxy-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene	

Compound No.	IUPAC Name	Structure
A96	4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-1-(1-methyl-3-azetidiny)-1H-1,2,3-triazole	
A97	(2S,3R)-2-methyl-1-{4-methyl-5-[1-(1-methyl-3-azetidiny)-1H-1,2,3-triazol-4-yl]-1,3a,6-triaza-7-indenyl}-3-azetidinol	
A98	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperaziny)-1-ethanone	
A99	2-(4-{7-[(S)-2-methyl-1-azetidiny]-4-methyl-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperaziny)-1-ethanone	
A100	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperaziny)-1-ethanone	
A101	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(3,3-dimethyl-1-piperaziny)-1-ethanone	
A102	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(S)-3-methyl-1-piperaziny]-1-ethanone	

Compound No.	IUPAC Name	Structure
A103	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(6,6-difluoro-1,4-diazepan-1-yl)-1-ethanone	
A104	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(S)-2-methyl-1-piperaziny]-1-ethanone	
A105	1-[(R)-2-methyl-1-piperaziny]-2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	
A106	1-[(R)-3-methyl-1-piperaziny]-2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	
A107	2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(2,2-dimethyl-1-piperaziny)-1-ethanone	
A108	1-[(2S,5R)-2,5-dimethyl-1-piperaziny]-2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	
A109	1-[(2R,5S)-2,5-dimethyl-1-piperaziny]-2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-(trifluoromethyl)-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	

Compound No.	IUPAC Name	Structure
A110	1-[(R)-3-methyl-1-piperazinyl]-2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	
A111	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(S)-3-methyl-1-piperazinyl]-1-ethanone	
A112	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(6,6-difluoro-1,4-diazepan-1-yl)-1-ethanone	
A113	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(3,3-dimethyl-1-piperazinyl)-1-ethanone	
A114	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(S)-2-methyl-1-piperazinyl]-1-ethanone	
A115	1-[(R)-2-methyl-1-piperazinyl]-2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	
A116	1-[(2R,5S)-2,5-dimethyl-1-piperazinyl]-2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-ethanone	

Compound No.	IUPAC Name	Structure
A117	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(2S,5R)-2,5-dimethyl-1-piperaziny]-1-ethanone	
A118	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(R)-2-(trifluoromethyl)-1-piperaziny]-1-ethanone	
A119	2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-[(S)-2-(trifluoromethyl)-1-piperaziny]-1-ethanone	
A120	(3S,4S)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A121	(3R,4R)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A122	(3R,4R)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A123	(3S,4S)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	

Compound No.	IUPAC Name	Structure
A124	(3R,4R)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A125	(3S,4S)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A126	(3R,4R)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A127	(3S,4S)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A128	(3R,4R)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A129	(3S,4S)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A130	(3R,4R)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	

Compound No.	IUPAC Name	Structure
A131	(3S,4S)-4-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-fluoro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A132	(3R,4R)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	
A133	(3S,4S)-4-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-4-methyl-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-methyl-3-pyrrolidinol	

[0043] In some cases, the compound is selected from (2S,3R)-1-{3-chloro-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol (A18); 7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene (A11); 7-[(S)-2-methyl-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene (A9); 7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene (A21); 2-(4-{7-[(R)-2-(trifluoromethyl)-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperaziny)-1-ethanone (A29); 7-[(S)-2-methyl-1-azetidiny]-3-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3a,6-triazaindene (A49); 2-(4-{7-[(S)-2-methyl-1-azetidiny]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl)-1-(1-piperaziny)-1-ethanone (A60); and 7-[(R)-2-(trifluoromethyl)-1-azetidiny]-4-methyl-5-[1-(1-methyl-3-azetidiny)-4-pyrazolyl]-1,3,3a,6-tetraazaindene (A89), or a pharmaceutically acceptable salt thereof.

a. General Synthetic Methods

[0044] Certain processes for the manufacture of the compounds of this disclosure are provided as further features of the disclosure and are illustrated by the following exemplary reaction schemes. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. For a more detailed description of the individual reaction steps, see the Examples section below. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art. In particular, it is noted that the compounds prepared according to these Schemes may be modified further to provide new Examples within the scope of this disclosure. In addition, it will be evident from the detailed

descriptions given in the Experimental section that the modes of preparation employed extend further than the general procedures described herein. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 2005, and "March's Advanced Organic Chemistry: Reactions Mechanisms and Structure", 8th Ed., Ed.: Smith, M.B., John Wiley & Sons, New York: 2019, the entire contents of which are hereby incorporated by reference.

[0045] The starting materials are generally available from commercial sources such as Merck Sigma-Aldrich Inc. and Enamine Ltd. Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including Supplements (also available via the Beilstein online database).

[0046] As an initial note, in the preparation of compounds of the present disclosure, it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in intermediates). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparative methods and can be readily determined by one of ordinary skill in the art. The use of such protection/deprotection methods is also within the ordinary skill in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991 and Greene's Protective Groups in Organic Synthesis, John Wiley & Sons, New York 2006.

[0047] For example, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl, benzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the Formula I compound.

b. General Synthetic Methods

[0048] Certain processes for the manufacture of the compounds of this disclosure are provided as further features of the disclosure and are illustrated by the following exemplary reaction schemes. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. For a more detailed description of the individual reaction steps; see the Examples section herein. Although specific starting materials and reagents are depicted in the schemes and discussed herein, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described herein can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art. In particular, it is noted that the compounds prepared according to these Schemes may be modified further to provide new Examples within the scope of this disclosure. In addition, it will be evident from the detailed

descriptions given in the Experimental section that the modes of preparation employed extend further than the general procedures described herein. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 2005, and "March's Advanced Organic Chemistry: Reactions Mechanisms and Structure", 8th Ed., Ed.: Smith, M.B., John Wiley & Sons, New York: 2019, the entire contents of which are hereby incorporated by reference.

[0049] The starting materials are generally available from commercial sources such as Merck Sigma-Aldrich Inc. and Enamine Ltd., Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including Supplements (also available via the Beilstein online database).

[0050] As an initial note, in the preparation of compounds of the present disclosure, it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in intermediates). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparative methods and can be readily determined by one of ordinary skill in the art. The use of such protection/deprotection methods is also within the ordinary skill in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991 and Greene's Protective Groups in Organic Synthesis, John Wiley & Sons, New York 2006.

[0051] For example, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl, benzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the Formula I compound.

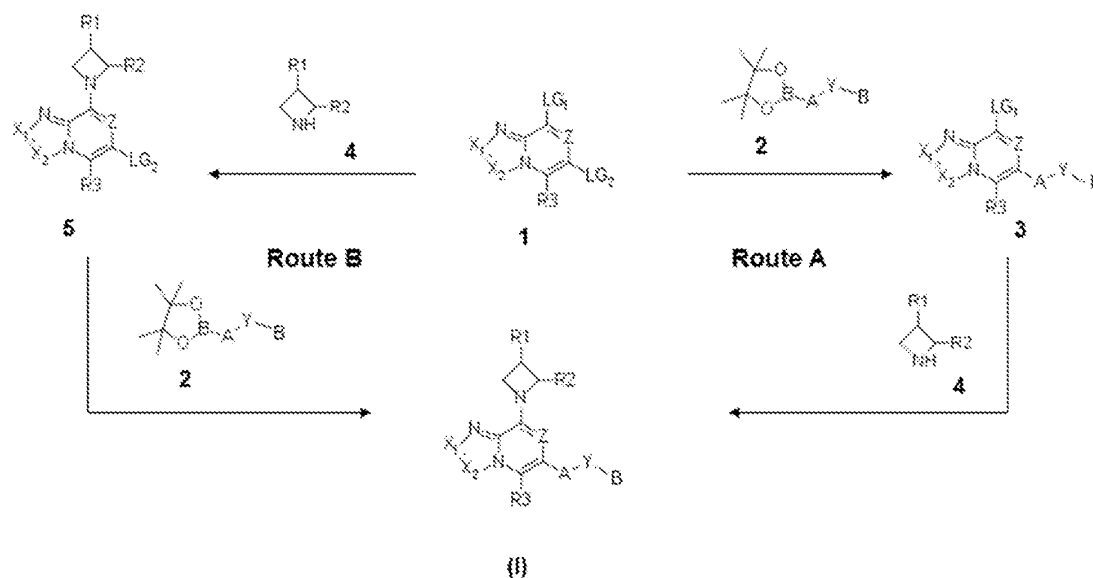
[0052] Compounds of Formula I, or salts thereof, may be prepared by a variety of methods known to those skilled in the art. Nonlimiting examples of these methods are outlined in the following schemes, preparations and examples. All substituents are as defined herein, unless indicated otherwise. Reagents, solvents and starting materials are commercially available, known in the literature or readily accessible to one skilled in the art. Products of each synthetic procedure can be recovered and isolated by conventional methods well known in the art, including extraction, evaporation, precipitation, chromatography, filtration, trituration and crystallization.

[0053] Compounds of Formula I may be isolated as racemates, enantiomers or diastereoisomers using well-known techniques such as crystallization, chiral chromatography, or supercritical fluid chromatography. These techniques may be applied at the appropriate point in the synthesis. The Formula I compound diastereomers/enantiomers can be

prepared as racemic mixtures followed by appropriate chiral separation as described herein or by for example reaction with the desired chiral substituted azetidine compound.

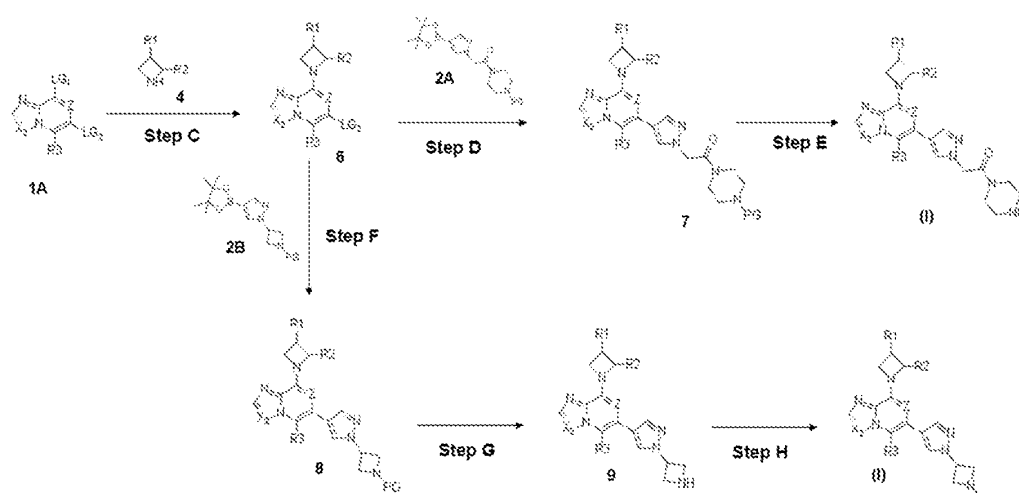
[0054] One skilled in the art will appreciate that compounds of Formula I, or salts thereof, can also be synthesized following similar methods to those described herein, with modifications, for example: a) the use of appropriate protection/deprotection strategies; b) the use of the appropriately substituted starting materials and reactants; c) appropriate changes to the order of synthetic steps; d) transformation of one functional group to another; e) use of an alternative stereochemical configuration.

[0055] Scheme 1:



[0056] Scheme 1 provides a general strategy for the preparation of compounds of Formula I. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I. Route A shows the conversion of bicyclic compound **1** to compound **3** by Suzuki coupling between boronate **2** and LG_1 of **1**. Nucleophilic aromatic substitution (SN_{Ar}) reaction of compound **3** (LG_1) with azetidine **4** provides compounds of Formula I. Route B shows an alternative strategy to convert bicyclic compound **1** to azetidine compound **5** by SN_{Ar} reaction between LG_1 of **1** and azetidine **4**. Subsequent Suzuki coupling of boronate **2** with **5** (LG_2) provides compounds of Formula I. The synthesis of compounds following these strategies utilises appropriately substituted reactants, appropriate protection/deprotection steps, and other functional group transformations, as necessary.

[0057] Scheme 2:

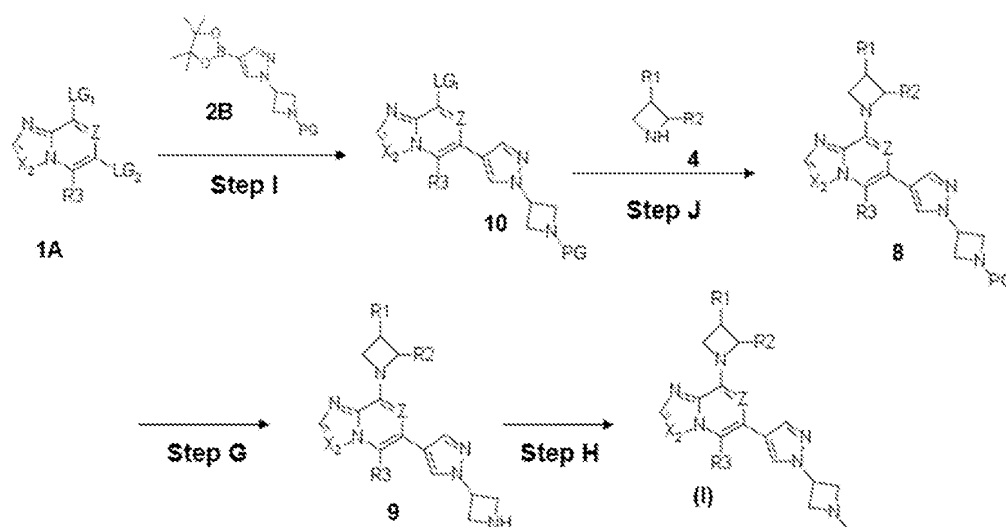


[0058] Scheme 2 shows one strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0059] In Step C, dihalo-bicyclic compound **1A** undergoes an S_NAr reaction with azetidine **4** to give azetidine compound **6**. Typical reaction conditions include a base, for example K_2CO_3 , in an organic solvent such as NMP, at elevated temperature. Compound **6** then undergoes a Suzuki reaction in Step D with boronate **2A** to give compound **7**. This reaction is performed with a base, for example Na_2CO_3 , in an organic solvent, for example 1,4-dioxane, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0), at elevated temperature. In Step E, compound **7** is deprotected, for example using TFA to remove a BOC group, to yield compounds of Formula I.

[0060] Compound **6** also undergoes a Suzuki reaction with boronate **2B** in Step F to afford pyrazole **8**. Reaction conditions are similar to those for Step D, using DTBPF $PdCl_2$ as the palladium catalyst. In Step G, compound **8** is deprotected, for example using TFA to remove a BOC group, to give compound **9**, which is then methylated in Step H to yield compounds of Formula I. Typical reaction conditions include the use of formaldehyde and a reducing agent, for example $NaBH(OAc)_3$, in an organic solvent such as dichloromethane at room temperature.

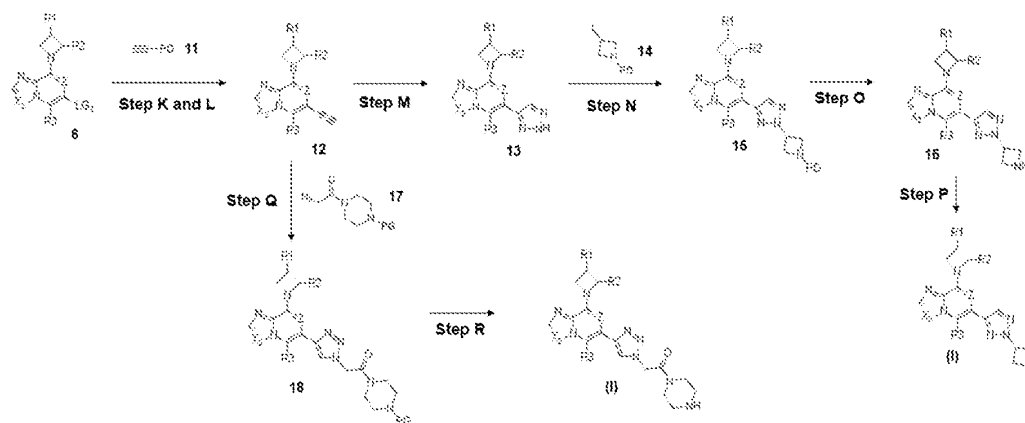
[0061] Scheme 3:



[0062] Scheme 3 shows another strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0063] In Step I, using similar conditions to Step F from Scheme 2, dihalo-bicyclic compound **1A** undergoes a Suzuki reaction with boronate **2B** to give compound **10**, which then undergoes an S_NAr reaction with azetidine **4** to give compound **8**. Typical reaction conditions include a base, for example triethylamine, in an organic solvent such as NMP, at elevated temperature. Compound **9** is deprotected, as described in Step G, Scheme 2, and then methylated, as described in Step H, Scheme 2, to provide compounds of Formula (I).

[0064] Scheme 4:

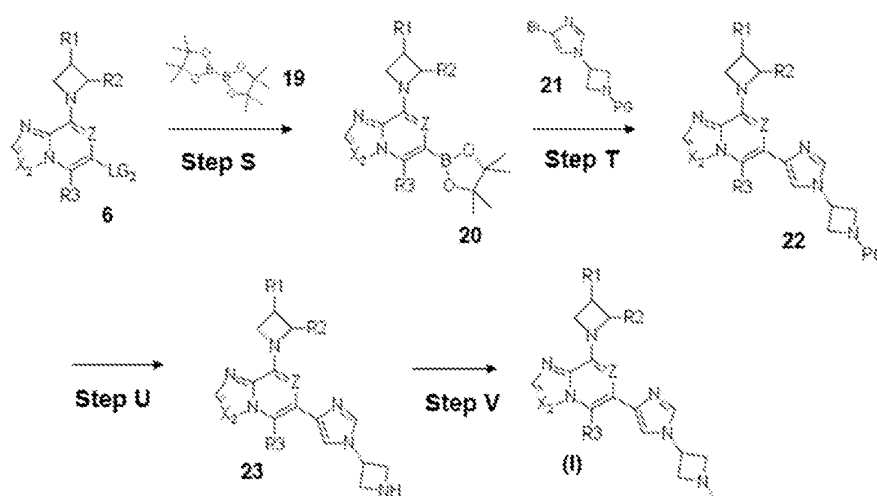


[0065] Scheme 4 shows a further strategy to synthesize a subset of compounds of Formula I. PG is defined as a protecting group, for example BOC or TMS, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0066] Azetidine compound **6** is made using methods described in Scheme 2. In Step K, azetidine compound **6** undergoes a cross-coupling reaction with alkyne **11**. This reaction is performed with a base, for example TEA, in the presence of a palladium catalyst, such as Pd(dppf)Cl₂, and a copper catalyst, such as copper (I) iodide at elevated temperature. The alkyne protecting group is then removed in Step L. Typical reaction conditions are using potassium hydroxide in methanol at room temperature to give compound **12**. In Step M, alkyne compound **12** undergoes a cycloaddition reaction with an azide, for example TMS-azide, to give triazole **13**. Typical reaction conditions include a base, for example sodium ascorbate, a copper catalyst, for example copper sulfate, in a solvent such as t-butanol/water, at elevated temperature. Compound **13** then undergoes an S_N2 displacement with iodo-azetidine **14** to give azetidine **15**. This reaction is performed in the presence of a base, such as caesium carbonate, in an organic solvent, such as DMF, at elevated temperature. Compound **15** is deprotected, as described in Step G, Scheme 2, and then methylated, as described in Step H, Scheme 2, to provide compounds of Formula (I).

[0067] Alkyne **12** also undergoes a cycloaddition reaction with azide **17** in Step Q to give triazole **18**. Typical reaction conditions use a copper catalyst, such as copper (I) iodide, a base, such as DIEA, in an organic solvent, such as THF, at ambient temperature. In Step R, compound **18** is deprotected, for example using TFA to remove a BOC group, to yield compounds of Formula (I).

[0068] Scheme 5:

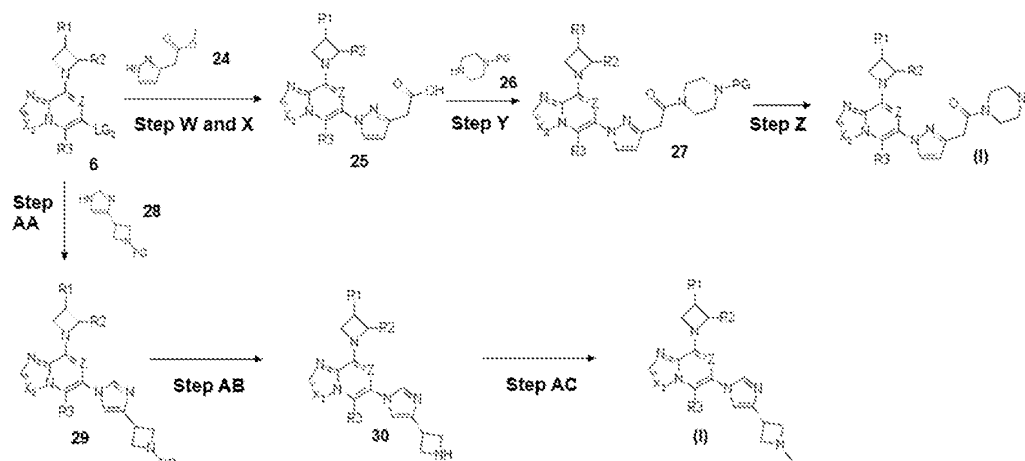


[0069] Scheme 5 shows a further strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0070] Azetidine compound **6** is made using methods described in Scheme 2. In Step S, azetidine **6** is transformed into boronate **20** through a cross coupling reaction with BDP. This reaction is performed in the presence of a base, such as potassium acetate, a palladium catalyst, such as XPhos Pd G4, in an organic solvent, such as dioxane, at elevated temperature. Boronate **20** subsequently undergoes a Suzuki coupling with bromo-imidazole **21** to give imidazole **22**. Typical reaction conditions are a palladium catalyst, such as SPhos Pd G2, a base, such as potassium phosphate, in a

solvent, such as THF/water, at elevated temperature. Compound **22** is deprotected to compound **23**, as described in Step G, Scheme 2, and then methylated, as described in Step H, Scheme 2, to provide compounds of Formula (I).

[0071] Scheme 6:

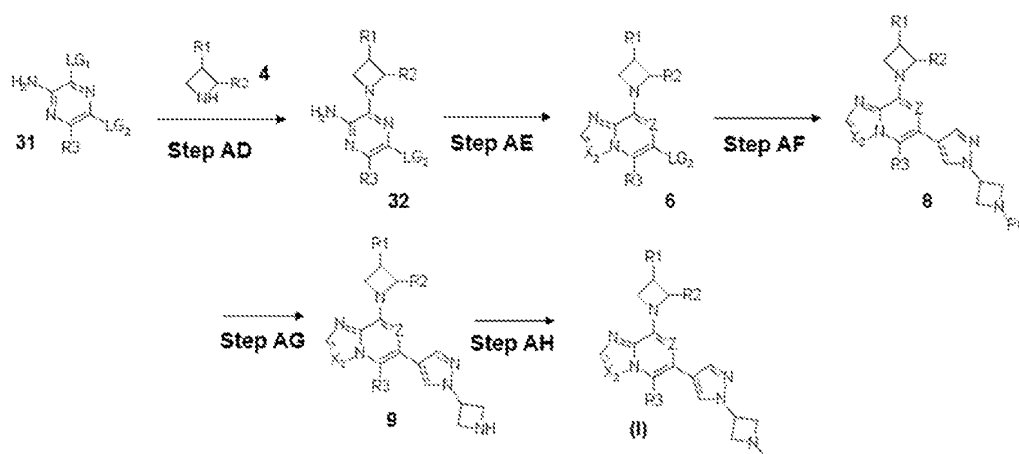


[0072] Scheme 6 shows a further strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0073] Azetidine compound **6** is made using methods described in Scheme 2. In Step W, compound **6** undergoes a coupling reaction between LG2 of **6** and pyrazole ester **24**. Typical conditions include a base, such as caesium carbonate, a copper catalyst, such as bis[(tetrabutylammonium iodide)copper (I) iodide], an amine ligand, such as DMDACH, in an organic solvent, such as dioxane, at elevated temperature. The resulting ester is then hydrolysed to pyrazole acid **25** in Step X using a base, such as lithium hydroxide, in a solvent such as THF/water, at elevated temperature. Acid **25** is coupled to a mono-protected piperazine **26** in Step Y to give piperazine amide **27** using standard amide forming reagents, such as HATU, and an organic base, such as DIEA, in an organic solvent, such as DMF, at ambient temperature. In Step Z, compound **27** is deprotected, for example using TFA to remove a BOC group, to yield compounds of Formula (I).

[0074] Compound **6** can also undergo coupling reactions in Step AA with imidazole **28**, under similar conditions to those described in Step W, to give imidazole **29**. Compound **29** is deprotected to amine **30**, as described in Step G, Scheme 2, and then methylated, as described in Step H, Scheme 2, to provide compounds of Formula (I).

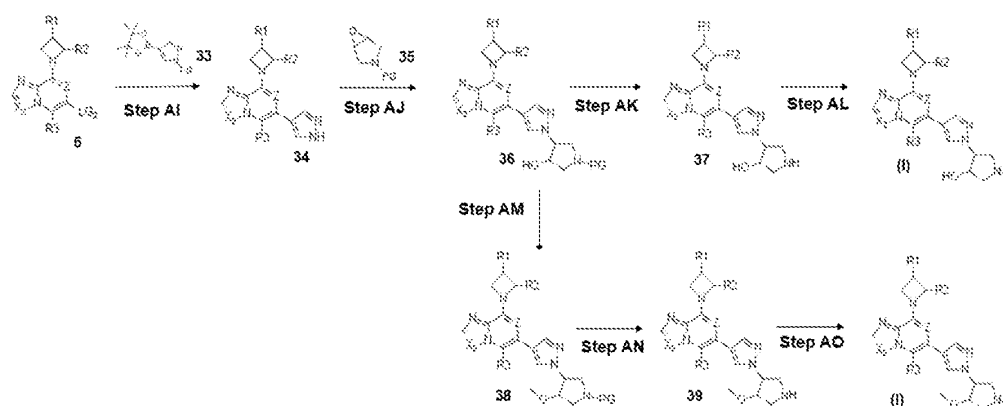
[0075] Scheme 7:



[0076] Scheme 7 shows a further strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0077] Azetidine compound **6** is made using methods described in Scheme 2. In Step AD, dihalo-pyrazine compound **31** undergoes an S_NAr reaction with azetidine **4** to give azetidine compound **32**. This reaction is performed in the presence of a base, such as potassium carbonate, in an organic solvent, such as THF, at elevated temperature. Amino pyrazine **32** undergoes cyclisation in Step AE to give bicyclic compound **6**. Typical reaction conditions include (i) 2-chloroacetaldehyde in a solvent, such as water/IPA, at elevated temperature; or (ii) 2-bromo-1,1-dimethoxy-ethane in a solvent, such as water/IPA, at elevated temperature. Compound **6** is then transformed in Steps AF, AG and AH into compounds of Formula (I), using similar conditions to Steps F, G and H in Scheme 2.

[0078] Scheme 8:



[0079] Scheme 8 shows a further strategy to synthesize a subset of compounds of Formula I. PG is defined as a nitrogen protecting group, for example BOC, which can be removed at an appropriate moment during the synthesis or at the end. LG is defined as a "leaving group", utilized in certain reactions for the synthesis of compounds of Formula I.

[0080] Azetidine compound **6** is made using methods described in Scheme 2. In Step AI, compound **6** undergoes a Suzuki coupling with boronate **33** to give pyrazole **34**; during this reaction the pyrazole protecting group is cleaved. Typical reaction conditions are a palladium catalyst, such as APHOS Pd G3, a base, such as caesium carbonate, in a solvent, such as dioxane/water, at elevated temperature. Pyrazole **34** undergoes an S_N2 displacement with epoxide **35** in Step AJ to give alcohol **36**. Typical reaction conditions include a base, such as caesium carbonate, an organic solvent, such as DMF, at elevated temperature. In Step AK, compound **36** is deprotected to amine **37**, as described in Step G, Scheme 2, and then methylated in Step AL, as described in Step H, Scheme 2, to provide compounds of Formula (I).

[0081] Alcohol **36** can additionally be methylated in Step AM to give ether **38** using an alkylating agent. Typical reaction conditions include methyl iodide, a base, such as sodium hydride, an organic solvent, such as DMF, at 0 °C to ambient temperature. Compound **38** is deprotected in Step AN to give amine **39**, as described in Step G, Scheme 2, and then methylated in Step AO, as described in Step H, Scheme 2, to provide compounds of Formula (I).

[0082] As can be appreciated by the skilled artisan, the foregoing synthetic Schemes and representative examples (herein) are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds. The disclosure further encompasses "intermediate" compounds, including structures produced from the synthetic procedures described, whether isolated or generated in-situ and not isolated, prior to obtaining the finally desired compound. These intermediates are included in the scope of this disclosure. Exemplary embodiments of such intermediate compounds are set forth in the Examples herein.

[0083] As can be appreciated by the skilled artisan, the above synthetic Schemes and representative examples (below) are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds. The disclosure further encompasses "intermediate" compounds, including structures produced from the synthetic procedures described, whether isolated or generated in-situ and not isolated, prior to obtaining the finally desired compound. These intermediates are included in the scope of this disclosure. Exemplary embodiments of such intermediate compounds are set forth in the Examples below.

Pharmaceutically Acceptable Salts

[0084] The compounds described herein can exist in free form, or, where appropriate, as salts. Those salts that are pharmaceutically acceptable are of particular interest since they are useful in administering the compounds described below for medical purposes. Salts that are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of the disclosure or intermediates thereof.

[0085] As used herein, the term "pharmaceutically acceptable salt" refers to salts of a compound which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue side effects, such as, toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[0086] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. These salts can be prepared in situ during the final isolation and purification of the compounds.

[0087] Where the compound described herein contains a basic group, or a sufficiently basic bioisostere, acid addition salts can be prepared by 1) reacting the purified compound in its free-base form with a suitable organic or inorganic acid and 2) isolating the salt thus formed. In practice, acid addition salts might be a more convenient form for use and use of the salt amounts to use of the free basic form.

[0088] Examples of pharmaceutically acceptable, non-toxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyroglutamate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0089] Other acids and bases, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid or base addition salts.

[0090] It should be understood that a compound disclosed herein can be present as a mixture/combination of different pharmaceutically acceptable salts. Also contemplated are mixtures/combinations of compounds in free form and pharmaceutically acceptable salts.

Prodrugs

[0091] The present disclosure also includes the prodrugs of compounds of Formula (I) (or any of the embodiments thereof described herein) and/or a pharmaceutically acceptable salt thereof. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient of Formula (I) (or any of the

embodiments thereof described herein) when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups, however, regenerate original functional groups *in vivo* or by routine manipulation. Prodrugs of compounds of Formula (I) (or any of the embodiments thereof described herein) include compounds wherein a hydroxy, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., *N,N*-dimethylaminocarbonyl) of hydroxy or amino functional groups in compounds of Formula (I)), amides (e.g., trifluoroacetyl amino, acetyl amino, and the like), and the like. Prodrugs of compounds of Formula (I) (or any of the embodiments thereof described herein) and/or a pharmaceutically acceptable salt thereof are also within the scope of this disclosure.

Metabolites

Also included within the scope of the disclosure are metabolites of compounds of Formula I, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the disclosure include

- (i) where the compound of Formula I contains a methyl group, an hydroxymethyl derivative thereof ($-\text{CH}_3 \rightarrow -\text{CH}_2\text{OH}$);
- (ii) where the compound of Formula I contains an alkoxy group, an hydroxy derivative thereof ($-\text{OR} \rightarrow -\text{OH}$);
- (iii) where the compound of Formula I contains a tertiary amino group, a secondary amino derivative thereof ($-\text{NRR} \rightarrow -\text{NHR}$ or $-\text{NHR}$);
- (iv) where the compound of Formula I contains a secondary amino group, a primary derivative thereof ($-\text{NHR} \rightarrow -\text{NH}_2$);
- (v) where the compound of Formula I contains a phenyl moiety, a phenol derivative thereof ($-\text{Ph} \rightarrow -\text{PhOH}$); and
- (vi) where the compound of Formula I contains an amide group, a carboxylic acid derivative thereof ($-\text{CONH}_2 \rightarrow -\text{COOH}$).

Hydrates and Solvates

[0092] The compounds described herein include hydrates and solvates of the compounds or pharmaceutically acceptable salts thereof. The term solvate is used herein to describe a molecular complex comprising the compound of the disclosure and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. Other solvents may be used as intermediate solvates in the preparation of more desirable solvates, such as methanol, methyl *t*-butyl ether, ethyl acetate, methyl acetate, (S)-propylene glycol, (R)-propylene glycol, 1,4-butyne-diol, and the like.

[0093] The term hydrate is employed when said solvent is water. Pharmaceutically acceptable solvates include hydrates and other solvates wherein the solvent of crystallization may be isotopically substituted, e.g., D₂O, d-acetone, d-DMSO. The solvates and/or hydrates preferably exist in crystalline form. A classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

[0094] Also included within the scope of the disclosure are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. The compounds of the disclosure may also exist as complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Halebian (August 1975).

[0095] The compounds of the disclosure may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins.

[0096] Polymorphs

The present disclosure also includes polymorphic forms (amorphous as well as crystalline).

[0097] The compounds of the disclosure may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

[0098] Certain compounds of the present disclosure or combination agents may exist in more than one crystal form (generally referred to as "polymorphs"). Polymorphs may be prepared by crystallization under various conditions, for example, using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and/or various modes of cooling, ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting the compound of the present disclosure followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Pharmaceutical Compositions

[0099] The compounds described herein can be formulated into pharmaceutical compositions that further comprise a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. In embodiments, the present disclosure relates to a pharmaceutical composition comprising a compound described above or salt thereof, and a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. In embodiments, the pharmaceutical composition comprises a safe and effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, adjuvant or vehicle. Pharmaceutically acceptable carriers include, for example, pharmaceutical diluents, excipients or carriers suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices.

[00100] An "effective amount" includes a "therapeutically effective amount" and a "prophylactically effective amount". The term "therapeutically effective amount" refers to an amount effective in treating and/or ameliorating diseases or disorders associated with KHK dysregulation in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing and/or substantially lessening the chances of developing diseases or disorders associated with KHK dysregulation.

[00101] A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, e.g., non-toxic, non-inflammatory, non-immunogenic or devoid of other undesired reactions or side-effects upon their administration to a subject. Standard pharmaceutical formulation techniques can be employed.

[00102] The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds described herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure. As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (e.g., a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily

adverse. An adverse effect from a therapy (e.g., prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Side effects include, but are not limited to fever, chills, lethargy, gastrointestinal toxicities (including gastric and intestinal ulcerations and erosions), nausea, vomiting, neurotoxicities, nephrotoxicities, renal toxicities (including such conditions as papillary necrosis and chronic interstitial nephritis), hepatic toxicities (including elevated serum liver enzyme levels), myelotoxicities (including leukopenia, myelosuppression, thrombocytopenia and anemia), dry mouth, metallic taste, prolongation of gestation, weakness, somnolence, pain (including muscle pain, bone pain and headache), hair loss, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances and sexual dysfunction.

[00103] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as tween 80, phosphates, glycine, sorbic acid, or potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, or zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, methylcellulose, hydroxypropyl methylcellulose, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00104] In some embodiments, the pharmaceutical compositions disclosed herein can be formulated with supplementary active ingredients.

[00105] The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as, for example, lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Preventing the action of microorganisms in the compositions disclosed herein is achieved by adding antibacterial and/or antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00106] In some embodiments, a pharmaceutical composition can be within a matrix which controls the release of the composition. In some embodiments, the matrix can comprise lipid, polyvinyl alcohol, polyvinyl acetate, polycaprolactone, poly(glycolic)acid, poly(lactic)acid, polycaprolactone, polylactic acid, polyanhydrides, polylactide-co-glycolides, polyamino acids, polyethylene oxide, acrylic terminated polyethylene oxide, polyamides, polyethylenes, polyacrylonitriles, polyphosphazenes, poly(ortho esters), sucrose acetate isobutyrate (SAIB), and combinations thereof and other polymers such as those disclosed, for example, in U.S. Pat. Nos. 6,667,371; 6,613,355; 6,596,296; 6,413,536; 5,968,543; 4,079,038; 4,093,709; 4,131,648; 4,138,344; 4,180,646; 4,304,767; 4,946,931, each of which is expressly incorporated by reference herein in its entirety. In these embodiments, the matrix sustainedly releases the drug.

[00107] Pharmaceutically acceptable carriers and/or diluents may also include any solvents, dispersion media, coatings, antibacterials and/or antifungals, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional medium or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions is contemplated.

[00108] In some embodiments, the pharmaceutical composition is in the form of an aqueous suspension, which can be prepared from solutions or suspensions. With respect to solutions or suspensions, dosage forms can be comprised of micelles of lipophilic substances, liposomes (phospholipid vesicles/membranes) and/or a fatty acid (e.g., palmitic acid). In particular embodiments, the pharmaceutical composition is a solution or suspension that is capable of dissolving in the fluid secreted by mucous membranes of the epithelium of the tissue to which it is administered, applied and/or delivered, which can advantageously enhance absorption.

[00109] The pharmaceutical composition can be an aqueous solution, a nonaqueous solution or a combination of an aqueous and nonaqueous solution. Suitable aqueous solutions include, but are not limited to, aqueous gels, aqueous suspensions, aqueous microsphere suspensions, aqueous microsphere dispersions, aqueous liposomal dispersions, aqueous micelles of liposomes, aqueous microemulsions, and any combination of the foregoing, or any other aqueous solution that can dissolve in the fluid secreted by the mucosal membranes of the nasal cavity. Exemplary nonaqueous solutions include, but are not limited to, nonaqueous gels, nonaqueous suspensions, nonaqueous microsphere suspensions, nonaqueous microsphere dispersions, nonaqueous liposomal dispersions, nonaqueous emulsions, nonaqueous microemulsions, and any combination of the foregoing, or any other nonaqueous solution that can dissolve or mix in the fluid secreted by mucosal membranes.

[00110] Examples of powder formulations include, without limitation, simple powder mixtures, micronized powders, freeze dried powder, lyophilized powder, powder microspheres, coated powder microspheres, liposomal dispersions, and any combination of the foregoing. Powder microspheres can be formed from various polysaccharides and celluloses, which include without limitation starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carbomer, alginate polyvinyl alcohol, acacia, chitosans, and any combination thereof.

[00111] The pharmaceutical composition can also optionally include an absorption enhancer, such as an agent that inhibits enzyme activity, reduces mucous viscosity or elasticity, decreases mucociliary clearance effects, opens tight junctions, and/or solubilizes the active compound. Chemical enhancers are known in the art and include chelating

agents (e.g., EDTA), fatty acids, bile acid salts, surfactants, and/or preservatives. Enhancers for penetration can be particularly useful when formulating compounds that exhibit poor membrane permeability, lack of lipophilicity, and/or are degraded by aminopeptidases. The concentration of the absorption enhancer in the pharmaceutical composition will vary depending upon the agent selected and the formulation.

[00112] To extend shelf life, preservatives can optionally be added to the pharmaceutical composition. Suitable preservatives include but are not limited to benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium chloride, and combinations of the foregoing. The concentration of the preservative will vary depending upon the preservative used, the compound being formulated, the formulation, and the like. In representative embodiments, the preservative is present in an amount of about 2% by weight or less.

[00113] As another option, the composition can comprise a flavoring agent, e.g., to enhance the taste and/or acceptability of the composition to the subject.

Routes of Administration and Dosages

[00114] The compounds and pharmaceutically acceptable compositions described above can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), or buccally. In some embodiments, the compound or composition disclosed herein is administered orally, via inhalation, or intravenously.

[00115] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00116] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00117] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00118] In order to prolong the effect of a compound described herein, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00119] Compositions for rectal or vaginal administration are specifically suppositories which can be prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00120] Solid dosage forms for oral administration include buccal films, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. In the case of buccal films, a film can employ a water-dissolving polymer, which allows the film to quickly hydrate, adhere, and dissolve when placed on the tongue, or in the oral cavity, which results in systemic drug delivery.

[00121] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be

used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00122] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00123] Dosage forms for topical or transdermal administration of a compound described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00124] Sterile injectable forms of the compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. 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 are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00125] The pharmaceutical compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include, but are not limited to, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00126] Alternatively, the pharmaceutical compositions described herein may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00127] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (as described herein) or in a suitable enema formulation. Topical application also includes the use of transdermal patches.

[00128] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2 octyldodecanol, benzyl alcohol and water.

[00129] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, specifically, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[00130] The pharmaceutical compositions may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00131] The compounds for use in the methods of the disclosure can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily dose or one of multiple daily doses (e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose.

Methods of Treatment

[00132] Provided herein are uses of a compound described herein as a therapeutic agent. The compounds described herein or pharmaceutically acceptable salts thereof can be used to inhibit ketohexokinase (KHK), and to treat or prevent diseases or disorders (e.g., wherein the diseases or disorders are associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol) in a biological sample (e.g., a cell culture) or in humans (e.g., in a subject). The compounds described herein or pharmaceutically acceptable salts thereof can be used in methods of treating or preventing diseases or disorders associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol. The compounds, pharmaceutical compositions, and methods of the present disclosure can be useful for treating a subject such as, but not limited to, a mammal, a human, a non-human mammal, a domesticated animal (e.g., laboratory animals, household pets, or livestock), a non-domesticated animal (e.g., wildlife), a dog, a cat, a rodent, a mouse, a hamster, a cow, a bird, a chicken, a fish, a pig, a horse, a goat, a sheep, or a rabbit, preferably a human. Thus, the compounds can be used to treat a disease, disorder, condition, or associated co-morbidity (referred to generally herein as a disease) selected from any one or more of the following: type 1 diabetes mellitus (T1D), type 2 diabetes mellitus (T2D), idiopathic T1D, latent autoimmune diabetes of adults (LADA), early-onset diabetes (EOD), atypical diabetes, maturity-onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, hyper-glycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, diabetic kidney disease (DKD), kidney disease, acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, obesity, eating disorders, excessive sugar craving, excessive alcohol consumption, dyslipidemia, hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, high non HDL cholesterol, low HDL cholesterol, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), MASLD with increased alcohol intake (MetALD), liver steatosis, fibrosis, cirrhosis, hepatocellular carcinoma, hereditary fructose intolerance (HFI), alcoholic steatohepatitis (ASH), viral liver disease, diseases associated with liver fibrosis or cirrhosis e.g. alpha-1 antitrypsin deficiency, hemochromatosis, pancreatic disorders including pancreatic cancer; gall bladder disease (PBC, PSC), coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, foot ulcerations, ulcerative colitis, hyperapobetalipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and irritable bowel syndrome. In some cases, the disclosure provides methods of treating metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver

disease (MASLD), MASLD with increased alcohol intake (MetALD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes mellitus (T2D), diabetic kidney disease (DKD), alcoholic steatohepatitis (ASH), alcohol-associated liver disease (ALD), liver fibrosis or cirrhosis, liver disease caused by hepatocellular stress, hereditary fructose intolerance, hyperuricemia, gout, addictive craving, a neurodegenerative disease, or cancer. In some cases, the disease or disorder is NASH or MASH.

[00133] In another embodiment, the disclosure provides a method of treating a disease selected from any one or combination of the following: T1D, T2D, insulin resistance, kidney disease, acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules, adipocyte dysfunction, visceral adipose deposition, obesity, eating disorders, excessive sugar craving, excessive alcohol consumption, dyslipidemia, hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, high non HDL cholesterol, low HDL cholesterol, NAFLD, MASLD, MetALD, liver steatosis, NASH, MASH, liver fibrosis, cirrhosis, hepatocellular carcinoma, HFK, hypertension, endothelial dysfunction, metabolic syndrome, hyperuricemia, and gout.

[00134] Preferred examples of diseases or disorders associated with KHK dysregulation include metabolic syndrome, NAFLD, NASH, MASLD, MASH, MetALD, T2D, hypertriglyceridemia, hypercholesterolemia, DKD, ASH, liver disease arising from hepatocyte stress (e.g. alpha-1 antitrypsin deficiency [AATD], viral hepatitis, or hemochromatosis), viral disease, addictive craving, alcohol use disorder, hyperuricemia, gout, a neurodegenerative disease, and cancer. In some cases, the disease or disorder is NASH or MASH.

[00135] KHK or fructokinase catalyzes the first step in fructose metabolism, phosphorylating fructose to fructose-1-phosphate (F1P) and depleting intracellular ATP and adenine nucleotide pool. There is no negative feedback mechanism by which F1P inhibits KHK metabolism of fructose, therefore accumulation of F1P is directly related to the amount of fructose either (1) transported into the cell via the GLUT transporters or (2) formed intracellularly from glucose via the polyol pathway, and metabolized via KHK. The accumulation of F1P and depletion of ATP and adenine nucleotide pool cause deleterious consequences in cells, tissues and organs, including oxidative stress, endothelial dysfunction, and metabolic dysregulation. Responses to these insults include lipogenesis and gluconeogenesis, which drive metabolic diseases. A patient experiencing KHK metabolism of fructose that occurs outside of normal parameters risks developing a disease or disorder resulting from the dysregulated state of KHK-mediated fructose metabolism, i.e., a disease or disorder associated with KHK dysregulation.

[00136] Non-limiting examples of diseases or disorders associated with excessive fructose intake, increased formation of fructose in hepatocytes via the polyol pathway (e.g. upon osmolar stress as with exposure to alcohol) or KHK dysregulation include metabolic syndrome and metabolic diseases (including type 2 diabetes mellitus (T2D) or hypertriglyceridemia), diseases of the liver [including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) and arising from hepatocyte stress (e.g. alpha-1 antitrypsin deficiency or hemochromatosis)], kidney diseases and disorders including diabetic kidney disease (DKD), addictive craving, alcohol use disorder, hyperuricemia, gout, a neurodegenerative disease (e.g., Parkinson's disease or Alzheimer's disease), and cancer. In some cases, the disease or disorder is NASH.

[00137] The terms, "disease", "disorder", and "condition" may be used interchangeably here to refer to medical or pathological condition associated with KHK dysregulation.

[00138] As used herein, the terms "subject" and "patient" are used interchangeably. The terms "subject" and "patient" refer to an animal (e.g., a bird such as a chicken, quail or turkey, or a mammal), specifically a "mammal" including a non-primate (e.g., a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (e.g., a monkey, chimpanzee and a human), and more specifically a human. The human may be a male or female. In one embodiment, the subject is a non-human animal such as a farm animal (e.g., a horse, cow, pig or sheep), or a pet (e.g., a dog, cat, guinea pig or rabbit). In a preferred embodiment, the subject is a "human".

[00139] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00140] KHK inhibition can be measured by any suitable method known in the art. For example, KHK inhibition in a biological sample (e.g. a cell culture or cell free isolated enzyme) or in humans (e.g. in a subject) can be measured. More specifically, for cell-based assays, in each case cells are cultured in vitro, a test agent is added to the culture, and after a suitable length of time an endpoint is evaluated. Such assays are known in the art.

[00141] As used herein, the terms "treat", "treatment" and "treating" refer to both therapeutic and prophylactic treatments. For example, therapeutic treatments include the reduction or mitigation of the progression, severity and/or duration of diseases or disorders associated with KHK dysregulation, or the amelioration of one or more symptoms (specifically, one or more discernible symptoms) of diseases or disorders associated with KHK dysregulation, resulting from the administration of one or more therapies (e.g., one or more therapeutic agents such as a compound or composition of the disclosure). In specific embodiments, the therapeutic treatment includes the amelioration of at least one measurable physical parameter of a diseases or disorders associated with KHK dysregulation. In other embodiments the therapeutic treatment includes the inhibition of the progression of a diseases or disorders associated with KHK dysregulation, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the therapeutic treatment includes the reduction or stabilization of diseases or disorders associated with KHK dysregulation.

[00142] The term "chemotherapy" refers to the use of medications, e.g., small molecule drugs (rather than "vaccines") for treating a disorder or disease.

[00143] The terms "prophylaxis" or "prophylactic use" and "prophylactic treatment" as used herein, refer to any medical or public health procedure whose purpose is to prevent, rather than treat or cure a disease. As used herein, the terms "prevent", "prevention" and "preventing" refer to the reduction in the risk of acquiring or developing a given condition, or the reduction or inhibition of the recurrence or said condition in a subject who is not ill. The term "chemoprophylaxis" refers to the use of medications, e.g. small molecule drugs (rather than "vaccines") for the prevention of a disorder or disease.

[00144] As used herein, prophylactic use includes the use in situations in which the presence of diseases or disorders associated with KHK dysregulation or fructose metabolism, including secondary to excessive consumption of fructose and/or alcohol has been detected. Prophylactic use may also include treating a person who is not ill with diseases or disorders associated with KHK dysregulation or not considered at high risk for complications, in order to reduce the chances of developing diseases or disorders associated with KHK dysregulation.

[00145] In some embodiments, the methods of the disclosure are a preventative or "prophylactic" measure to a patient, specifically a human, having a predisposition to complications resulting from diseases or disorders associated with KHK dysregulation.

[00146] As used herein, an "effective amount" refers to an amount sufficient to elicit the desired biological response. In the present disclosure the desired biological response is to inhibit KHK in a biological sample or a subject, or to reduce or ameliorate the severity, duration, progression, or onset of a disease or disorder associated with KHK dysregulation, prevent the advancement of a disease or disorder associated with KHK dysregulation, prevent the recurrence, development, onset or progression of a symptom associated with a disease or disorder associated with KHK dysregulation, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy used against diseases or disorders associated with KHK dysregulation. The precise amount of compound administered to a subject will depend on the mode of administration, the type and severity of disease or disorder and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When co-administered with other agents, e.g., when co-administered with another medication, an "effective amount" of the second agent will depend on the type of drug used. Suitable dosages are known for approved agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound described herein being used. In cases where no amount is expressly noted, a safe and effective amount should be assumed. For example, compounds described herein can be administered to a subject in a dosage range from between approximately 0.01 to 100 mg/kg body weight/day for therapeutic or prophylactic treatment.

[00147] Generally, dosage regimens can be selected in accordance with a variety of factors including the disease or disorder being treated and the severity of the disease or disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the renal and hepatic function of the subject; and the particular compound or salt thereof employed, the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The skilled artisan can readily determine and prescribe the effective amount of the compounds described herein required to treat, to prevent, inhibit (fully or partially) or arrest the progress of the disease or disorder.

[00148] Dosages of the compounds for uses described herein can range from between about 0.01 to about 100 mg/kg body weight/day, about 0.01 to about 50 mg/kg body weight/day, about 0.1 to about 50 mg/kg body weight/day, or about 1 to about 25 mg/kg body weight/day. It is understood that the total amount per day can be administered in a

single dose or can be administered in multiple dosing, such as twice a day (e.g., every 12 hours), three times a day (e.g., every 8 hours), or four times a day (e.g., every 6 hours).

[00149] For therapeutic treatment, the compounds described herein can be administered to a patient within, for example, 48 hours (or within 40 hours, or less than 2 days, or less than 1.5 days, or within 24 hours) of onset of symptoms. The compounds described herein can be also administered to a patient beyond this timeline, for example, within two weeks, six months, one year, five years, or ten years of onset of symptoms. The therapeutic treatment can last for any suitable duration, for example, for 5 days, 7 days, 10 days, 14 days, etc. For prophylactic treatment, the compounds described herein can be administered to a patient for any suitable duration, for example, for 7 days, 10 days, 14 days, 20 days, 28 days, 35 days, 42 days, etc.

Combination Therapy

[00150] The compounds described herein can be used in combination therapy, i.e., in conjunction with drugs, or in conjunction with a vaccine.

[00151] A safe and effective amount can be achieved in the method or pharmaceutical composition of the disclosure employing a compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof alone or in combination with an additional suitable therapeutic agent, for example, a drug or a vaccine. When "combination therapy" is employed, a safe and effective amount can be achieved using a first amount of a compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof, and a second amount of an additional suitable therapeutic agent (e.g., a drug or vaccine).

[00152] In embodiments, the compound of Formula (I) or Table A, or a pharmaceutically acceptable salt, and the additional therapeutic agent, are each administered in a safe and effective amount (i.e., each in an amount which would be therapeutically effective if administered alone). In other embodiments, the compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent, are each administered in an amount which alone does not provide a therapeutic effect (a sub-therapeutic dose). In yet other embodiments, the compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof can be administered in a safe and effective amount, while the additional therapeutic agent is administered in a sub-therapeutic dose. In still other embodiments, the compound of Formula (I) or Table A, a pharmaceutically acceptable salt thereof can be administered in a sub-therapeutic dose, while the additional therapeutic agent, is administered in a safe and effective amount.

[00153] Nonlimiting examples of additional therapeutic agents that can be administered to a subject comprise anti-diabetic agents, anti-obesity agents, anti-hypertensive agents, anxiolytic agents, antidepressants, agents to treat diabetic nephropathy, agents to treat diabetic neuropathy, cholesterol/lipid modifying agents, calcium channel blockers, cardiac glycosides, diuretics, anti-platelet agents, anti-coagulants, anti-osteoporosis agents, anti-inflammatory agents, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, anti-ulcer and gastroesophageal reflux disease agents, hormone replacement therapies, fructose transporter inhibitors, aldose reductase inhibitors, xanthine oxidase inhibitors, drugs for treating bile duct or gallbladder diseases (e.g., primary biliary cholangitis or primary sclerosing cholangitis) and viral liver diseases, therapeutics for treating AATD and hemochromatosis, drugs for treating heart

failure particularly preserved ejection heart failure, and agents for the treatment of MASH or NASH. Other nonlimiting examples of additional therapeutic agents that can be administered with compounds disclosed herein (e.g., compounds of Formula I or Table A) include those disclosed in US Patent No. 10,174,007, incorporated herein by reference. In some cases, the additional therapeutic agent comprises metformin, a fructose transporter inhibitor, an aldose reductase inhibitor, a xanthine oxidase inhibitor, a thyroid hormone beta-receptor agonist, an incretin hormone receptor agonist or modulator, or a sodium/glucose transporter inhibitor. In some cases, the incretin hormone receptor agonist or modulator is semaglutide, dulaglutide, liraglutide, tirzepatide, survodutide, retatrutide, pemvidutide, VK2735, orforglipron, cagrilintide/semaglutide, danuglipron, maridebart cafraglutide, RGT-075, PF-0695422, NN9487, NN9541, CT-388, CT-868, CT-996, efinopegdutide, efocipegtrutide, AZD9550, DR10624, NLY01, ECC5004, mazdutide, exenatide, TERN-601, ecnoglutide, or XW-004. In some cases, the fructose transporter inhibitor is an inhibitor of GLUT2, GLUT5, or both. In some cases, the aldose reductase inhibitor is AT-001, AT-003, gavoirestat, ranirestat, epalrestat, fidarestat, imirestat, tolrestat, or risarestat.

[00154] In some cases, compounds of Formula I or Table A, or a pharmaceutically acceptable salt, may be co-administered with one or more anti-diabetic agent selected from the group consisting of metformin, sulfonylureas (e.g., glipizide, glimepiride, glipentide, and tolbutamide), thiazolidinediones or peroxisome proliferator activating receptor gamma (PPAR γ) agonists (e.g., pioglitazone), DPP4 inhibitors (e.g., sitagliptin, linagliptin, vildagliptin, and saxagliptin), meglitinides, insulin and insulin analogs or mimetics, and inhibitors of SGLT1 and/or SGLT2 (e.g., dapagliflozin, empagliflozin, tofogliflozin, canagliflozin, ertugliflozin, and sotagliflozin). In some cases, compounds of Formula I or Table A, or a pharmaceutically acceptable salt, may be co-administered with one or more anti-obesity agent selected from the group consisting of amylin analogs (e.g., cagrilintide, pramlintide, AZD6234, LY3841136, amycretin, petrelintide, NN9487, and LY3541105), incretin hormone receptor agonists or modulators (e.g., semaglutide, liraglutide, tirzepatide, survodutide, retatrutide, pemvidutide, VK2735, RGT-075, cagrilintide/semaglutide, danuglipron, PF-0695422, NN9487, NN9541, CT-388, CT-868, CT-996, orforglipron, efinopegdutide, efocipegtrutide, AZD9550, DR10624, NLY01, maridebart cafraglutide, ECC5004, mazdutide, exenatide, dulaglutide, TERN-601, ecnoglutide, and XW-004), melanocortin 4 receptor agonists (e.g., setmelanotide), leptin receptor agonists (e.g., metreleptin and mibavademab), anti-GIPR mAbs, and activin type II receptor antagonists or ligand traps (e.g., bimagrumab, taldefgrobep alfa, trevogrumab, garetosmab, apitegromab, and SRK-439).

[00155] In some cases, compounds of Formula I or Table A or a pharmaceutically acceptable salt, may be co-administered with one or more cholesterol or lipid modifying agent selected from the group consisting of HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, rosuvastatin, simvastatin, and fluvastatin), cholesteryl ester transfer protein inhibitors (e.g., obicetrapib and dalcetrapib), ezetimibe, and PCSK9 inhibitors or modulators (e.g., alirocumab, evolocumab, inclisiran, tafolecimab, recaticimab, AZD-0780, VERVE-102, MK-0616). In some cases, compounds of Formula I or Table A, or a pharmaceutically acceptable salt, may be co-administered with one or more agents for the treatment of NAFLD, MASLD, NASH, or MASH selected from the group consisting of FGF21 analogs (e.g., efruxifermin, pegozafermin, BOS-580, B1344, BI3006337, NN9500, NN9499, and HEC8843), thyroid hormone beta-receptor agonists (e.g., resmetirom, VK2809, ASC41, TERN-501, and ALG-055009), incretin hormone receptor

agonists or modulators, PPAR agonists (e.g., pioglitazone, lanifibranor, PXL-065, and saroglitazar), FASN inhibitors (e.g., denifanstat), acetyl CoA carboxylase inhibitors (e.g., firsocostat and clesacostat), inhibitors or modulators of DGAT1 and/or DGAT2 (e.g., ervogostat, SNP-610, SNP-630, ION224, and PF-07202954), inhibitors or modulators of PNPLA3 (e.g., ALN-PNP, AZD-2693, PF-07853578, LY3849891, JNJ-75220795, and AMG609), alpha-1 antitrypsin enzyme replacement therapies, base editing or siRNA or RNAi or antisense therapies for the treatment of alpha-1 antitrypsin deficiency (e.g., fazirsiran, belcesiran, ALN-AAT, NTLA-2003, WVE-006, BEAM-302, and KRRO-110), anti-retroviral therapies for the treatment of HCV or HBV, and inhibitors or modulators of HSD17B13 (e.g., rapirosiran, INI-822, ARO-HSD, and AZD-7503).

[00156] In some cases, compounds of Formula I or Table A or a pharmaceutically acceptable salt, may be co-administered with the fructose transporter inhibitor which is an inhibitor of GLUT2, GLUT5, or both. In some cases, compounds of Formula I or Table A or a pharmaceutically acceptable salt, may be co-administered with the aldose reductase inhibitor AT-001, AT-003, gavorestat, ranirestat, epalrestat, fidarestat, imirestat, tolrestat, or risarestat.

[00157] As used herein, the terms "in combination" or "co-administration" can be used interchangeably to refer to the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). The use of the terms does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject.

[00158] Coadministration encompasses administration of the first and second amounts of the compounds of the coadministration in an essentially simultaneous manner, such as in a single pharmaceutical composition, for example, capsule or tablet having a fixed ratio of first and second amounts, or in multiple, separate capsules or tablets for each. In addition, such coadministration also encompasses use of each compound in a sequential manner in either order.

[00159] In embodiments, the present disclosure is directed to methods of combination therapy for inhibiting KHK in biological samples or patients, or for treating or preventing diseases or disorders associated with KHK dysregulation in patients using the compounds or pharmaceutical compositions described herein, e.g., a compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof. Accordingly, pharmaceutical compositions also include those comprising a compound as disclosed herein in combination with one or more additional therapeutic or prophylactic agents for treating or preventing a disease or disorder associated with KHK dysregulation.

[00160] Methods of use of the compounds and compositions disclosed herein also include combination of chemotherapy with a compound or composition of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof or with a combination of a compound or composition of this disclosure with another therapeutic or prophylactic agent.

[00161] When co-administration involves the separate administration of the first amount of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof and a second amount of an additional therapeutic agent, the compounds are administered sufficiently close in time to have the desired therapeutic effect. For example, the period of time between each administration which can result in the desired therapeutic effect, can range from minutes to hours and can be determined taking into account the properties of each compound such as potency, solubility, bioavailability, plasma half-life and kinetic profile. For example, a compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof and the second therapeutic agent can be administered in any order within about 24 hours of each other, within about 16

hours of each other, within about 8 hours of each other, within about 4 hours of each other, within about 1 hour of each other or within about 30 minutes of each other.

[00162] More, specifically, a first therapy (e.g., a prophylactic or therapeutic agent such as a compound of the disclosure) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to a subject.

[00163] It is understood that the method of co-administration of a first amount of a compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof and a second amount of an additional therapeutic agent can result in an enhanced or synergistic therapeutic effect, wherein the combined effect is greater than the additive effect that would result from separate administration of the first amount of the compound of Formula (I) or Table A, or a pharmaceutically acceptable salt thereof and the second amount of the additional therapeutic agent.

[00164] As used herein, the term "synergistic" refers to a combination of a compound disclosed herein and another therapy (e.g., a prophylactic or therapeutic agent), which is more effective than presumed additive effects of the therapies. A synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) can permit the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject. The ability to utilize lower dosages of a therapy (e.g., a prophylactic or therapeutic agent) and/or to administer said therapy less frequently can reduce the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, management or treatment of a disorder. In addition, a synergistic effect can result in improved efficacy of agents in the prevention, management or treatment of a disorder. Finally, a synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

[00165] The presence of a synergistic effect can be determined using suitable methods for assessing drug interaction. Suitable methods include, for example, the Sigmoid-Emax equation (Holford, N.H.G. and Scheiner, L.B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median-effect equation (Chou, T. C. and Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)). Each equation referred to above can be applied with experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

Chiral Separations

[00166] The compounds described herein can have asymmetric centers and occur as racemates, racemic mixtures, individual diastereomers or enantiomers, with all isomeric forms being included in the present disclosure. Compounds of

the present disclosure having a chiral center can exist in and be isolated in optically active and racemic forms. Some compounds can exhibit polymorphism. The present disclosure encompasses racemic, optically-active, polymorphic, or stereoisomeric forms, or mixtures thereof, of a compound of the disclosure, which possess the useful properties described herein. The optically active forms can be prepared by, for example, resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase or by enzymatic resolution. One can either purify the respective compound, then derivatize the compound to form the compounds described herein, or purify the compound themselves.

[00167] Certain stereospecific stereoisomers or diastereomers are typically conveniently prepared with a stereospecific substituted azetidine compound resulting in the desired azetidiny bicyclic compound. The hydroxymethyl azetidine precursor stereochemistry preparation is known from the literature (J. Med. Chem. 2020, 63, 13546-13560). The methyl azetidine precursor enantiomer may be obtained from commercial sources. The stereochemistry of the azetidine stereocenters is retained during combination with the bicycles and during further derivatization. Accordingly, the stereochemistry of the desired Formula I stereoisomers and diastereomers is known. Alternative substituted bicyclic compounds may also be combined with the stereospecific substituted azetidine compounds to achieve the desired Formula I compounds (or further derivatized) as described in the examples (e.g., Ex. 1). Certain compounds of Formula I have "B" ring stereochemistry. As noted in the Table D Examples those compounds' (e.g., Ex. 120-133) B ring absolute stereochemistry has been assigned arbitrarily. While the stereochemistry is assigned arbitrarily the compounds are absolutely identified through a combination of the LCMS and ¹H NMR data.

[00168] Optically active forms of the compounds can be prepared using any method known in the art, including but not limited to by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase.

[00169] Examples of methods to obtain optically active materials include at least the following.

- i) physical separation of crystals: a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, *i.e.*, the material is a conglomerate, and the crystals are visually distinct;
- ii) simultaneous crystallization: a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;
- iii) cocrystallization: a technique whereby the individual enantiomers are crystallized together from a solution of the racemate;
- iv) enzymatic resolutions: a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;
- v) enzymatic asymmetric synthesis: a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;
- vi) chemical asymmetric synthesis: a synthetic technique whereby the desired enantiomer is synthesized

from an achiral precursor under conditions that produce asymmetry (*i.e.*, chirality) in the product, which can be achieved using chiral catalysts or chiral auxiliaries;

vii) diastereomer separations: a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

viii) first- and second-order asymmetric transformations: a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

ix) kinetic resolutions: this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

x) enantiospecific synthesis from non-racemic precursors: a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

xi) chiral liquid chromatography: a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase (including but not limited to via chiral HPLC). The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xii) chiral gas chromatography: a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xiii) extraction with chiral solvents: a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiv) transport across chiral membranes: a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through.

[00170] Chiral chromatography, including but not limited to simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

[00171] The present disclosure will be better understood with reference to the following non-limiting examples.

Abbreviations

TFA: trifluoroacetic acid

LC/MS: liquid chromatography mass spectrometry

HPLC: high performance liquid chromatography

min: minutes

NMP: 1-methyl-2-pyrrolidinone

DCM: dichloromethane

DIEA: N,N-diisopropylethylamine

TLC: thin layer chromatography

NMR: nuclear magnetic resonance

RT: retention time

DTBPF: 1,1'-bis(di-tert-butylphosphino)ferrocene

CSA: Camphor sulfonic acid

DMSO: dimethylsulfoxide

EA: ethyl acetate

NIS: N-iodosuccinimide

DMF: dimethylformamide

THF: tetrahydrofuran

Selectfluor: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

SPhos Pd G2: Chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

TsOH: 4-toluenesulfonic acid

ACN: acetonitrile

TMS: trimethylsilyl

DAST: (diethylamino)sulfur trifluoride

DPPF: 1,1'-ferrocenediyl-bis(diphenylphosphine)

TFAA: trifluoroacetic anhydride

IPA: isopropyl alcohol

XPhos Pd G4: (SP-4-3)-[Dicyclohexyl[2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]-2-yl]phosphine](methanesulfonato-κO)[2'-(methylamino-κN)[1,1'-biphenyl]-2-yl-κC]palladium

DMDACH: dimethylcyclohexane-1,2-diamine

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

NBS: N-bromosuccinimide

TBSOTf: tert-Butyldimethylsilyl trifluoromethanesulfonate

TBAF: tetrabutylammonium fluoride

DMAP: N,N-Dimethylpyridin-4-amine

t-Bu XPhos: 2-Di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl

TEA: triethylamine

Py: pyridine

Bpin: pinacoloboron

SFC: super-critical fluid chromatography

DMF-DMA: N,N-Dimethylformamide dimethyl acetal

Eaton's reagent: Phosphorus pentoxide, 7.7 wt. % in methanesulfonic acid

BPD: Bis(pinacolato)diboron

Compound Synthesis

[00172] The following preparations of compounds of Formula (I) and intermediates are given to enable those skilled in the art to more clearly understand and to practice the present disclosure. They should not be considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof.

[00173] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this disclosure can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[00174] Compound names were generated using ChemDraw® software.

[00175] The following LC/MS conditions are referred to in the synthetic examples below.

[00176] Method A: 5-95AB_3.5min: LC/MS The column used for chromatography was a 5µm C18 90A, 30*3.0 mm. Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 50-2000. Mobile phase A was 0.04% trifluoroacetic acid (TFA) in water, and mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The gradient was 5-95% B in 3.50 min. 5% B in 0.01 min, 5-95% B (0.01-2.50 min) with a hold at 95% B for 0.50 min, 95-5% B (3.00-3.01 min) with a hold at 5% B for 0.49 min. The flow rate was 1 mL/min (0.01-3.00 min)-1.2 mL/min (3.01-3.50 min).

[00177] Method B: 10-100AB_2MIN: LC/MS The column used for chromatography was a C18 5µm, 3.0*30mm (5µm particles). Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 100-1000. Mobile phase A was 0.04% TFA in water, and mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The gradient was 10-100% B in 1.30 min. 10% B in 0.01 min, 10-100% B (0.01-0.70 min) with a hold at 100% B for 0.60 min. The flow rate was 1.5 mL/min (0.00-1.30 min).

[00178] Method C: 5-95AB_2min: LC/MS The column used for chromatography was a 5µm C18 90A, 30*3.0mm. Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 50-2000. Mobile phase A was 0.04% TFA in water, and mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The gradient was 5-95% B in 1.50 min. 5% B in 0.01 min, 5-95% B (0.01-0.70 min), 95%B for 0.46 min. 95-5% B (1.61-1.50 min) with a hold at 5% B for 0.11 min. The flow rate was 1.5 mL/min.

[00179] Method D: 10-100AB_1MIN: LC/MS The column used for chromatography was a C18 3.0*30mm, 5µm. Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 50-2000. Mobile phase A was 0.04% TFA in water, and mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The gradient was 10-100% B in 0.90 min. 10% B in 0.01 min, 10-100% B (0.01-0.50 min) with a hold at 100% B for 0.40 min. The flow rate was 2.0 mL/min.

[00180] Method E: 5_95AB_6min-220-254-ELSD: LC/MS The gradient: 5% B in 0.01 min, 5-95% B (0.01-1.60 min), 95-100% B (1.60-2.50 min), 100-5% (2.50-2.52 min) with a hold at 5% B for 0.48 min. The flow rate was 0.8 mL/min. Mobile phase A was 0.037% TFA in water, mobile phase B was 0.018% TFA in HPLC-grade acetonitrile. The column used for chromatography was a C18 3.0*30mm, 2.5µm column (2.5µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive electrospray ionization. MS range was 100-1000.

[00181] Method F: 5_95CD_6min-220-254-ELSD: LC/MS The gradient was 5%B in 0.40min and 5-95% B at 0.40-3.40 min, hold on 95%B for 0.45min, and then 95-5%B in 0.01 min, the flow rate was 0.8 mL/min. Mobile phase A was 10mM ammonium bicarbonate in water, mobile phase B was Acetonitrile. The column used for chromatography was a C18 2.1*50mm column (5µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection. MS mode was positive electrospray ionization. MS range was 100-1000.

[00182] Method G: 5-95CD_2min: LC/MS The column used for chromatography was C18 2.1*50mm, (5 μ m particles). Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 100-1000. Mobile phase A was 10 mM ammonium bicarbonate in water, and mobile phase B was HPLC-grade acetonitrile. The gradient was 5-95% B in 1.50 min. 5% B in 0.01 min, 5-95% B (0.01-0.70 min), 95%B for 0.46 min. 95-5% B (1.61-1.50 min) with a hold at 5% B for 0.11 min. The flow rate was 1.5 mL/min.

[00183] Method H: 5-95AB_0.8min: Mobile phase: Ramp from 5% acetonitrile (0.01875% TFA) in water (0.0375% TFA) to 95% acetonitrile in water in 0.60 min, flow rate is set at 2.0 mL/min; then hold at 95% acetonitrile for 0.18 minutes, flow rate is set at 2.0 mL/min; return back to 5% acetonitrile in water and hold for 0.02 min. Flow rate is set at 2.0 mL/min. Column temperature at 50°C. The column is C18 2.1x30mm 5 μ m.

[00184] Method I: 5_95AB_6min-220-254-ELSD: LC/MS The gradient was 5%B in 0.40min and 5-95% B in 2.60 min, hold on 95% B in 1.00 min, and then 95-5%B in 0.01 min, the flow rate was 1.0 mL/min. Mobile phase A was 0.04% TFA in water, mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The column used for chromatography was a C18 50*2.0mm column (5 μ m particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection. MS mode was positive electrospray ionization. MS range was 100-1000.

[00185] Method J: 5_95AB_6min-220-254: LC/MS The gradient was 5%B in 0.40 min and 5-95% B in 2.60 min, hold on 95% B in 1.00 min, and then 95-5%B in 0.01 min, the flow rate was 1.0 mL/min. Mobile phase A was 0.04% TFA in water, mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The column used for chromatography was a C18 50*2.0mm column (5 μ m particles). Detection methods are diode array (DAD) detection. MS mode was positive electrospray ionization. MS range was 100-1000.

[00186] Method K: 10-80AB_10min: LC/MS The gradient was 10-80% B in 8.00 min with a hold at 80% B for 2.00 min, 80-10% B in 0.01 min, and then held at 10% for 2.99 min (0.5mL/min flow rate). Mobile phase A was 0.04% TFA in water, mobile phase B was 0.02% TFA in HPLC-grade acetonitrile. The column used for chromatography was a Halo AQ-C18 3.0x100mm column (2.7 μ m particles). Detection methods are diode array (DAD) .MS mode was positive electrospray ionization. MS range was 100-1000.

[00187] Method L: 10-80CD_10min: LC/MS The gradient was 10-80% B in 8.00 min with a hold at 80% B for 2.00 min, 80-10% B in 0.01 min, and then held at 10% for 2.99 min (0.5 mL/min flow rate). Mobile phase A was 10mM ammonium bicarbonate in water, mobile phase B was HPLC-grade acetonitrile. The column used for chromatography was XBridge C18 3.0*100mm,3.5 μ m. Detection methods are diode array (DAD). MS mode was positive electrospray ionization. MS range was 50-2000.

[00188] Method M: POS-NEG-10-100CD_1min: LC/MS The column used for chromatography was Xtimate C18 2.1*30mm, 5 μ m. Detection methods are diode array (DAD). MS mode was positive electrospray ionization and negative electrospray ionization acquisition simultaneously. MS range was 50-2000. Mobile phase A was 10 mM ammonium bicarbonate in water, and mobile phase B was HPLC-grade acetonitrile. The gradient was 10-100% B in 0.90 min. 10% B in 0.01 min, 10-100% B (0.01-0.50 min) with a hold at 100% B for 0.40 min. The flow rate was 1.5 mL/min (0.00-0.90 min).

[00189] Method N: 5-95AB_0.8 min: Mobile phase: ramp from 0% acetonitrile (0.01875% TFA) in water (0.0375% TFA) to 60% acetonitrile in water in 0.60 min. Flow rate is set at 2.0 mL/min; then hold at 60% acetonitrile for 0.18 minutes. Flow rate is set at 2.0 mL/min; return back to 0% acetonitrile in water and hold for 0.02 min. Flow rate is set at 2.0 mL/min. Column temperature at 50°C. The column is of Kinetex® EVO C18 2.1x30 mm 5 µm.

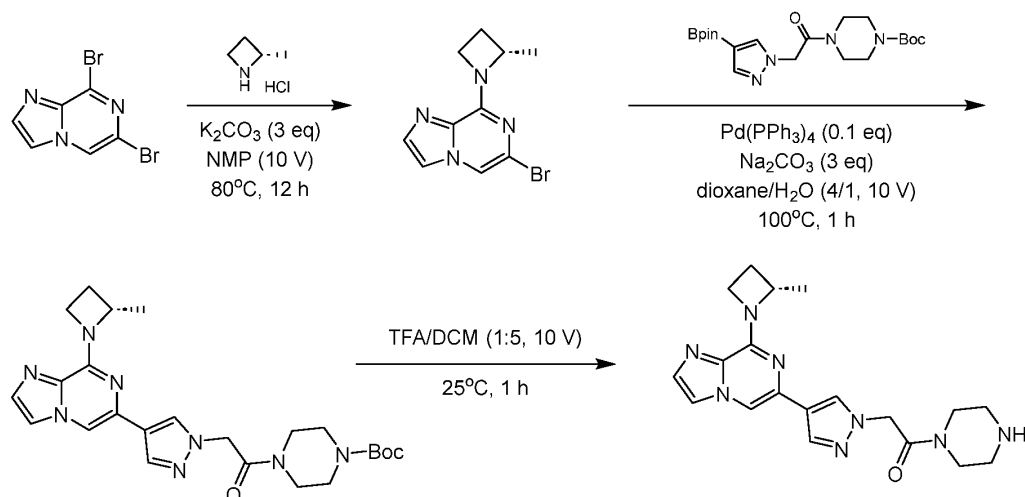
[00190] Method O: 10-80AB_6 min: Mobile phase: Ramp from 10% acetonitrile (0.01875%TFA) in water (0.0375% TFA) to 80% acetonitrile in 4.8 min. Flow rate is set at 0.7 mL/min; then hold at 80% acetonitrile for 0.60 minutes. Flow rate is set at 1.0 mL/min; return back to 10% acetonitrile in water and hold for 0.60 min. Flow rate is set at 1.0 mL/min. Column temperature at 50°C. The column is of ZORBAX SB-C18 2.1x50 mm 1.8 µm 600 Bar

[00191] Method P: Table B

TABLE B

Instrument		Agilent 1260 LC & Agilent 6125C MSD		
Software		Agilent Open Lab CDS 2.6		
HPLC	Column	Agilent poroshell 120 EC-C18 3.0×50 mm,2.7 µm		
	Mobile Phase	A: 0.0375% TFA in water (v/v)		
		B: 0.01875% TFA in Acetonitrile (v/v)		
	Gradient	Time (min)	B (%)	Flow (mL/min)
		0.00	05	1.0
		0.40	05	1.0
		3.00	99	1.0
		4.00	99	1.0
		4.10	5	1.0
		4.50	5	1.0
	Post time(min)	Off		
	Column Temp	45°C		
	Detector	DAD		
MS	Ionization source	ESI		
	Drying Gas	N ₂		
	Drying Gas Flow	10 (L/min)		
	Nebulizer Pressure	40 (psi)		
	Drying Gas Temperature	350 °C		
	Capillary Voltage	3500 (V) Positive		
	MS Polarity	Positive		

	MS Mode	Scan
	Mass Range	100-2000

EXAMPLE 1: Synthesis of Compound A1

[00192] Synthesis of tert-butyl 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate

[00193] To a solution of 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetic acid (CAS # 1083326-41-3, 8.50 g, 33.72 mmol, 1 eq) in DMF (85 mL) was added tert-butyl piperazine-1-carboxylate (6.28 g, 33.72 mmol, 1 eq), DIEA (13.07 g, 101.16 mmol, 17.62 mL, 3 eq) and HATU (19.23 g, 50.58 mmol, 1.5 eq). The mixture was exchanged with N₂ three times and was stirred at 25°C for 1 h under N₂ protection. TLC and LCMS showed all starting material was consumed and new product was formed. The reaction mixture was quenched by addition of water (50 mL). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 3:1 to 0:1, (TLC: petroleum ether:ethyl acetate = 0:1, R_f=0.7) to give tert-butyl 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetyl]piperazine-1-carboxylate (7.2 g, 50.8%).

[00194] LCMS (ESI+): m/z 421.2 (M+H)⁺, RT: 0.689 min (Method B)

[00195] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.84 (s, 1 H) 7.56 (s, 1 H) 5.16 (s, 2 H) 3.35 – 3.54 (m, 8 H) 1.42 (s, 9 H) 1.26 (s, 12 H)

[00196] Synthesis of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00197] To a solution of 6,8-dibromimidazo[1,2-a]pyrazine (CAS # 63744-22-9, 0.5 g, 1.81 mmol, 1 eq) in NMP (5 mL) was added K₂CO₃ (0.73 g, 5.43 mmol, 3 eq) and (2S)-2-methylazetidine (227.12 mg, 2.17 mmol, 1.2 eq, HCl salt,

CAS # 935669-67-3). The mixture was stirred at 80°C for 12 h. LCMS showed desired compound was detected. The reaction mixture was diluted with H₂O (10 mL) and extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with NaCl (40 mL) twice, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 100:0 to 1:1, (TLC: petroleum ether:ethyl acetate = 1:1, R_f=0.4) to give 6-bromo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (64%).

[00198] LCMS (ESI+): m/z 269.0 (M+H)⁺, RT: 0.699 min (Method C)

[00199] ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 7.81 (s, 1 H) 7.70 (s, 1 H) 7.48 (d, J=0.86 Hz, 1 H) 4.87 - 4.85 (m, 1 H) 4.47 - 4.63 (m, 1 H) 4.31 - 4.43 (m, 1 H) 2.57 - 2.68 (m, 1 H) 2.04 - 2.11 (m, 1 H) 1.59 (d, J=6.24 Hz, 3 H)

[00200] Synthesis of tert-butyl (S)-4-(2-(4-(8-(2-methylazetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate

[00201] To a solution of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (0.3 g, 1.12 mmol, 1 eq) in dioxane (2.4 mL) and H₂O (0.6 mL) was added tert-butyl 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (372.33 mg, 1.12 mmol, 1 eq) and Na₂CO₃ (357.10 mg, 3.37 mmol, 3 eq) and Pd(PPh₃)₄ (129.78 mg, 112.31 μmol, 0.1 eq). The mixture was stirred at 100°C for 1 h. LCMS showed desired compound was detected. The reaction mixture was diluted with H₂O (20 mL) and extracted with ethyl acetate (20 mL) twice. The combined organic layers were washed with aqueous NaCl (20 mL) four times, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 100:0 to 43:57, (TLC: petroleum ether:ethyl acetate = 1:2, R_f=0.3) to give tert-butyl (S)-4-(2-(4-(8-(2-methylazetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)acetyl)piperazine-1-carboxylate (0.115 g, 15%).

[00202] LCMS (ESI+): m/z 481.4 (M+H)⁺, RT: 0.586 min (Method C)

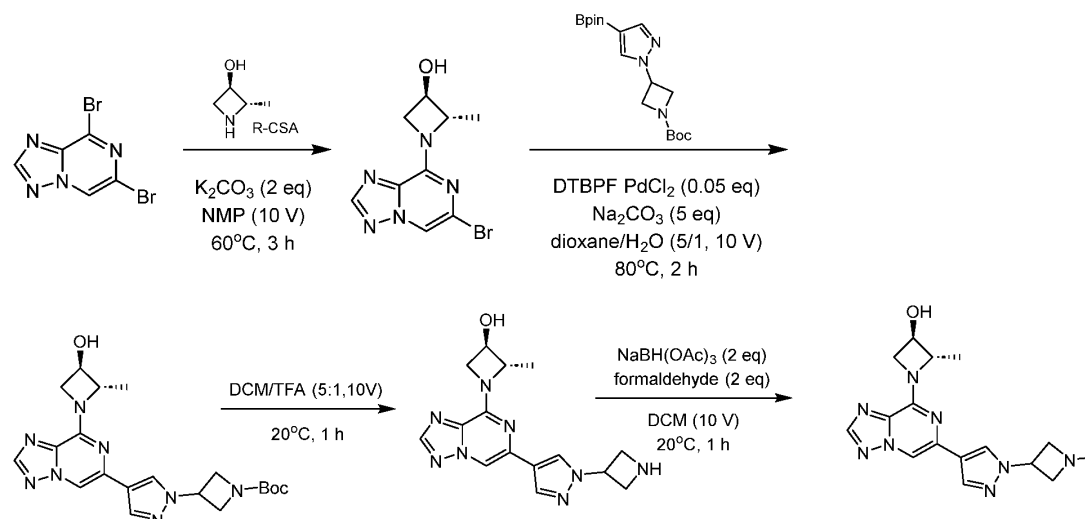
[00203] Synthesis of (S)-2-(4-(8-(2-methylazetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one

[00204] To a solution of tert-butyl 4-[2-[4-[8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate (0.1 g, 208.09 μmol, 1 eq) in DCM (0.83 mL) was added TFA (0.17 mL). The mixture was stirred at 25°C for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with NH₄Cl solution (10 mL) and extracted with ethyl acetate (5 mL). The combined organic layers were washed with aqueous NaCl (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: C18 150*40mm*10μm; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 15%-45% B over 8 min) to give (S)-2-(4-(8-(2-methylazetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (22 mg, 26%).

[00205] LCMS (ESI+): m/z 381.2 (M+H)⁺, RT: 2.152 min (Method F)

[00206] ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 8.04 (d, $J=1.25$ Hz, 2 H) 7.93 (s, 1 H) 7.74 (d, $J=0.88$ Hz, 1 H) 7.51 (d, $J=1.00$ Hz, 1 H) 5.20 (s, 2 H) 4.90 - 4.93 (m, 1 H) 4.53 - 4.66 (m, 1 H) 4.28 - 4.44 (m, 1 H) 3.55 - 3.67 (m, 4 H) 2.77 - 3.05 (m, 4 H) 2.50 - 2.71 (m, 1 H) 2.02 - 2.31 (m, 1 H) 1.65 (d, $J=6.25$ Hz, 3 H)

EXAMPLE 2: Synthesis of Compound A2



[00207] Synthesis of (2S, 3R)-1-(6-bromo-[1, 2, 4]triazolo[1,5-a]pyrazin-8-yl)-2-methylazetidin-3-ol

[00208] To a solution of 6,8-dibromo-[1,2,4]triazolo[1,5-a]pyrazine (CAS# 944709-42-6, 250 mg, 899.58 μmol , 1 eq) in N-methyl-2-pyrrolidone (2.5 mL) was added potassium carbonate (248.65 mg, 1.80 mmol, 2 eq) and (2S,3R)-2-methylazetidin-3-ol (156.75 mg, 1.8 mmol, 2 eq, R-CSA salt; synthesized as described in J. Med. Chem. 2020, 63, 13546–13560, intermediate 13/(R)-CSA salt). The mixture was stirred at 60°C for 3 h. TLC (petroleum ether:ethyl acetate = 3:1, $R_f=0.3$) showed all starting material was consumed and one new product generated. The reaction mixture was quenched by addition of water (10 mL) at 25°C, and then extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2 , petroleum ether/ethyl acetate = 3/1) to give (2S,3R)-1-(6-bromo-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)-2-methylazetidin-3-ol (190 mg, 74%).

[00209] Synthesis of tert-butyl 3-[4-[8-[(2S, 3R)-3-hydroxy-2-methyl-azetidin-1-yl]-[1,2,4]triazolo [1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00210] A mixture of (2S,3R)-1-(6-bromo-[1,2,4]triazolo[1,5-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (190 mg, 668.75 μmol , 1 eq), tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate [CAS 877399-35-4] (116.77 mg, 334.37 μmol , 0.5 eq), 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (24.47 mg, 33.44 μmol , 0.05 eq), sodium carbonate (354.40 mg, 3.34 mmol, 5 eq) in a mixture of dioxane (1.6 mL) and water (0.4 mL) was degassed and purged with nitrogen three times, and then the mixture was stirred at 80°C for 2 h under nitrogen atmosphere. LCMS showed starting material was consumed completely and desired mass was detected. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (6 mL). The organic phase was separated,

washed with ethyl acetate (10 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 3/1) to give tert-butyl 3-[4-[8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (100 mg, 35%).

[00211] LCMS (ESI+): m/z 427.1 (M+H)⁺, RT: 0.400 min (Method H)

[00212] ¹H NMR (DMSO-d₆, 400 MHz) δ 8.63 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 5.73 (d, 1H, J = 6.5 Hz), 5.2-5.3 (m, 1H), 4.62 (br s, 1H), 4.42 (br s, 1H), 4.2-4.3 (m, 2H), 4.1-4.2 (m, 3H), 4.0-4.1 (m, 1H), 1.61 (br d, 3H, J = 6.4 Hz), 1.42 (s, 9H)

[00213] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00214] To a solution of tert-butyl 3-[4-[8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (100 mg, 164.52 μmol, 1 eq) in dichloromethane (0.9 mL) was added trifluoroacetic acid (0.2 mL). The mixture was stirred at 20°C for 1 hr. TLC (petroleum ether:ethyl acetate = 0:1, R_f = 0.1) showed all starting material was completely consumed and one new product generated. The reaction mixture was quenched by addition of water (3 mL) at 20°C and adjusted to pH = 10 with aqueous sodium carbonate, and then extracted with dichloromethane (5 mL × 3). The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol. It was used for the next step directly without purification.

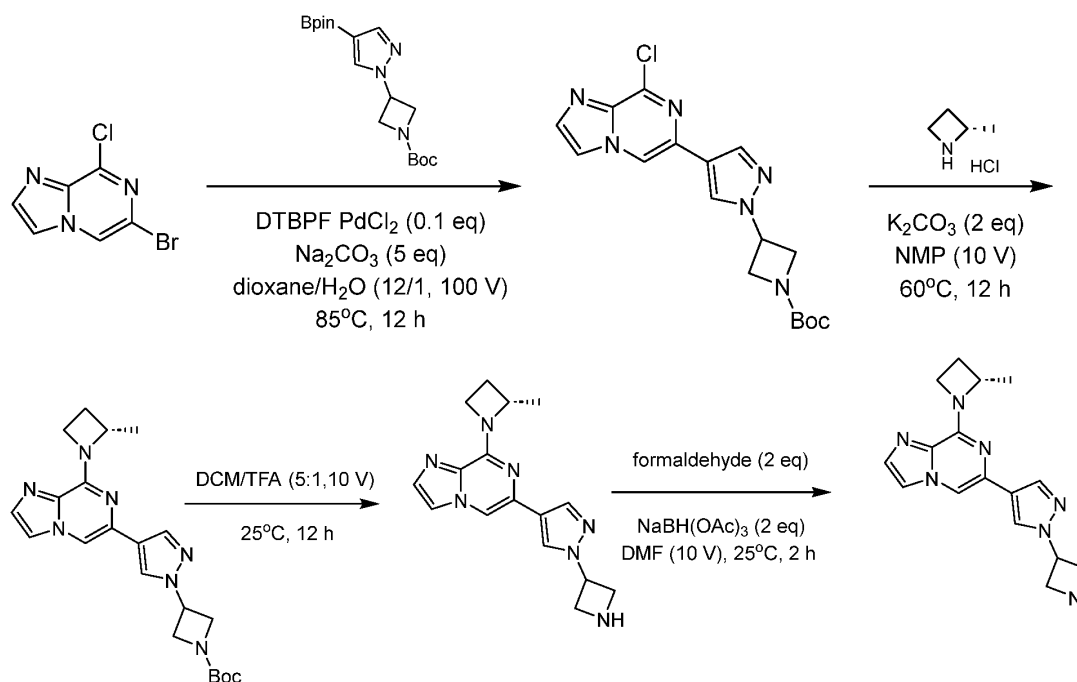
[00215] Synthesis of (2S,3R)-2-methyl-1-[6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]azetidin-3-ol

[00216] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (50 mg, 153.21 μmol, 1 eq) in dichloromethane (5 mL) was added sodium triacetoxy borohydride (97.41 mg, 459.62 μmol, 3 eq) and formaldehyde (24.87 mg, 306.41 μmol, 22.81 μL, 37% purity, 2 eq). The mixture was stirred at 20°C for 1 h. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (trifluoroacetic acid condition, column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water(trifluoroacetic acid)- acetonitrile]; gradient: 6%-36% B over 10 min) to give (2S,3R)-2-methyl-1-[6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazin-8-yl]azetidin-3-ol (15 mg, 29%).

[00217] LCMS (ESI+): m/z 341.1 (M+H)⁺, RT: 0.244 min (Method H)

[00218] ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.67 (1 H, s), 8.48 (1 H, s), 8.31 (1 H, s), 8.25 (1 H, s), 5.75 (1 H, br s), 5.36 - 5.50 (1 H, m), 4.27 - 4.80 (6 H, m), 4.19 (1 H, br d, J = 4.00 Hz), 4.03 (1 H, m), 2.99 (3 H, br s), 1.61 (3 H, br d, J = 6.38 Hz)

EXAMPLE 3: Synthesis of Compound A3



[00219] Synthesis of tert-butyl 3-[4-(8-chloroimidazo[1,2-a]pyrazin-6-yl)pyrazol-1-yl]azetidine-1-carboxylate

[00220] To a solution of 6-bromo-8-chloro-imidazo[1,2-a]pyrazine (CAS # 1208083-37-7; 1 g, 4.30 mmol, 1 eq) in dioxane (96 mL) and H₂O (4 mL) was added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (1.50 g, 4.30 mmol, 1 eq), Na₂CO₃ (2.28 g, 21.51 mmol, 5 eq) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (280.36 mg, 430.17 μmol, 0.1 eq). The mixture was exchanged with N₂ three times and was stirred at 85°C for 12 h under N₂ protection. TLC and LCMS showed all starting material was consumed and a new product formed. The reaction mixture was quenched by addition of H₂O (100 mL) at 25°C and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 1:0 to 0:1, (TLC: petroleum ether:ethyl acetate = 0:1, R_f=0.38) to give tert-butyl 3-[4-(8-chloroimidazo[1,2-a]pyrazin-6-yl)pyrazol-1-yl]azetidine-1-carboxylate (300 mg, 19%).

[00221] LCMS (ESI+): m/z 375.1 (M+H)⁺, RT: 2.262 min (Method A)

[00222] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.23 (s, 1 H), 8.13 (s, 1 H), 7.93 (s, 1 H), 7.83 (d, J = 0.88 Hz, 1 H), 7.77 (d, J = 0.88 Hz, 1 H), 5.11 (tt, J = 7.85, 5.41 Hz, 1 H), 4.33 - 4.47 (m, 4 H), 1.47 - 1.50 (m, 9 H)

[00223] Synthesis of tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00224] To a solution of tert-butyl 3-[4-(8-chloroimidazo[1,2-a]pyrazin-6-yl)pyrazol-1-yl]azetidine-1-carboxylate (300 mg, 800.38 μmol, 1 eq) in NMP (3 mL) was added (2S)-2-methylazetidine (62.62 mg, 800.38 μmol, 1 eq, HCl salt) and

K₂CO₃ (221.24 mg, 1.60 mmol, 2 eq). The reaction mixture was stirred at 60°C for 12 h. TLC and LCMS showed all starting material was consumed and a new product was formed. The reaction mixture was quenched by addition of H₂O (5 mL) at 25°C, and extracted with EA (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 1:0 to 0:1, (TLC: petroleum ether:ethyl acetate = 0:1, R_f=0.24) to give tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (300 mg, 92%).

[00225] LCMS (ESI+): m/z 410.2 (M+H)⁺, RT: 2.066 min (Method A)

[00226] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.92 (s, 1 H), 7.88 (s, 1 H), 7.64 (s, 1 H), 7.52 (s, 1 H), 7.45 (s, 1 H), 5.09 (quin, J=6.66 Hz, 1 H), 4.86 - 4.97 (m, 1 H), 4.55 - 4.65 (m, 1 H), 4.31 - 4.49 (m, 5 H), 2.53 - 2.66 (m, 1 H), 2.06 - 2.13 (m, 1 H), 1.69 (d, J=6.11 Hz, 3 H), 1.48 (s, 9 H)

[00227] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00228] To a mixture of tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (300 mg, 732.63 μmol, 1 eq) in DCM (5 mL) was add TFA (0.5 mL), and the mixture was stirred at 25°C for 12 h. LCMS showed one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (200 mg, 88%) which was used in the next step without further purification.

[00229] LCMS (ESI+): m/z 310.2 (M+H)⁺, RT: 1.309 min (Method A)

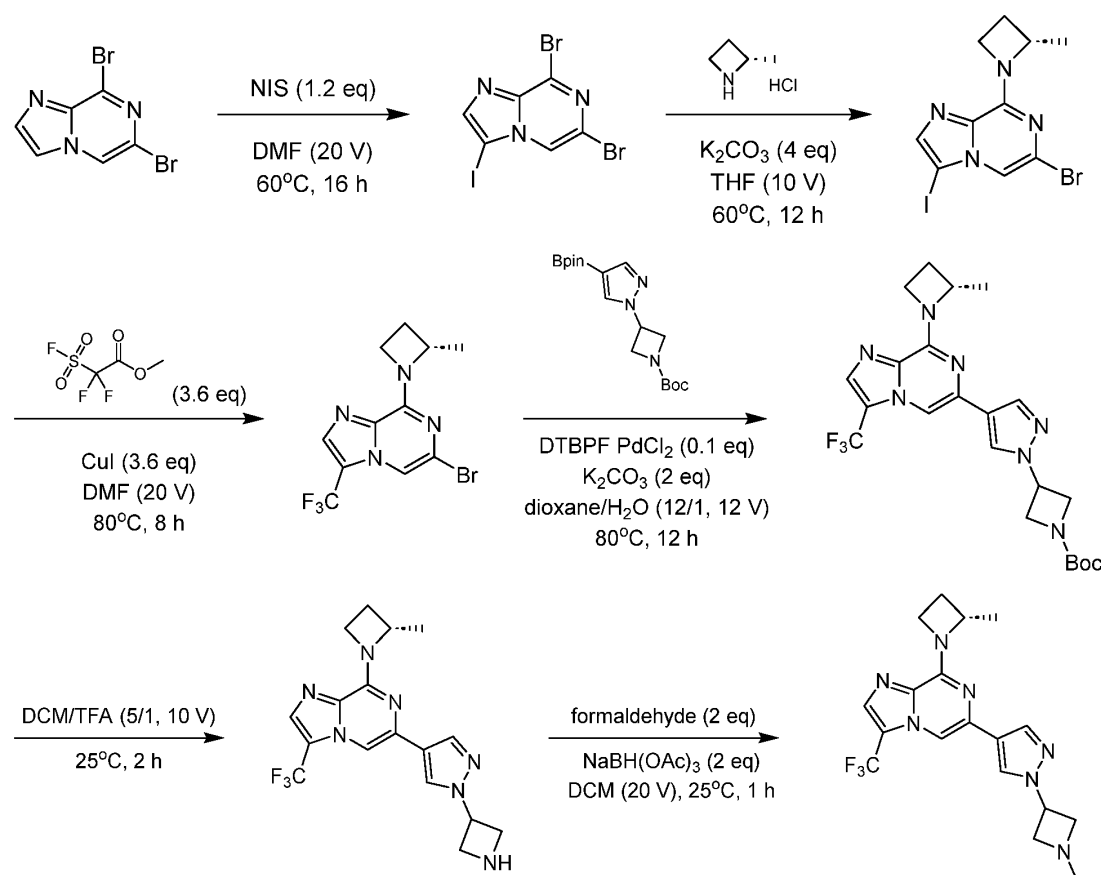
[00230] ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.20 (s, 1 H), 8.08 (s, 1 H), 8.04 (s, 1 H), 8.00 (d, J=1.25 Hz, 1 H), 7.83 (d, J=1.25 Hz, 1 H), 5.45 - 5.57 (m, 1 H), 5.24 - 5.35 (m, 1 H), 4.73 - 4.84 (m, 1 H), 4.59 (d, J=7.38 Hz, 5 H), 2.77 - 2.91 (m, 1 H), 2.22 (ddt, J=11.07, 9.38, 5.66, 5.66 Hz, 1 H), 1.76 (d, J=6.38 Hz, 3 H)

[00231] Synthesis of 8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine

[00232] A mixture of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (50 mg, 161.62 μmol, 1 eq) and formaldehyde (9.71 mg, 323.24 μmol, 8.91 μL, 2 eq) in DMF (1 mL) was stirred at 25°C for 0.5 h, then NaBH(OAc)₃ (68.51 mg, 323.24 μmol, 2 eq) was added, and the reaction mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass was detected. The reaction mixture was purified by prep-HPLC (twice, column: Agela DuraShell NH₂ 150mm*30mm*5μm; mobile phase: [Heptane-EtOH]; gradient:5%-70% B over 10.0 min) to give 8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine (5 mg, 10%).

[00233] LCMS (ESI+): m/z 324.1 (M+H)⁺, RT: 2.396 min (Method E)

[00234] ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.12 (s, 1 H), 8.01 (s, 1 H), 7.95 (s, 1 H), 7.72 (d, J=1.00 Hz, 1 H), 7.49 (d, J=1.00 Hz, 1 H), 5.01 - 5.11 (m, 1 H), 4.89 - 4.93 (m, 1 H), 4.58 (td, J=8.91, 5.44 Hz, 1 H), 4.36 (td, J=9.10, 6.69 Hz, 1 H), 3.84 - 3.93 (m, 2 H), 3.66 (br t, J=7.57 Hz, 2 H), 2.54 - 2.66 (m, 1 H), 2.50 (s, 3 H), 2.09 (ddt, J=10.79, 9.19, 6.27 Hz, 1 H), 1.64 (d, J=6.25 Hz, 3 H)

EXAMPLE 4: Synthesis of Compound A4

[00235] Synthesis of 6,8-dibromo-3-iodo-imidazo[1,2-a]pyrazine

[00236] To a solution of 6,8-dibromoimidazo[1,2-a]pyrazine (1 g, 3.61 mmol, 1 eq) in DMF (20 mL) was added NIS (974.94 mg, 4.33 mmol, 1.2 eq). The mixture was exchanged with N₂ three times and was stirred at 60°C for 16 h under N₂ protection. TLC and LCMS showed all starting material was consumed and a new product formed. The reaction mixture was quenched by addition of water (20 mL). The mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with petroleum ether:ethyl acetate = 10:1 at 25°C for 120 min to give 6,8-dibromo-3-iodo-imidazo[1,2-a]pyrazine (1.1 g, 76%).

[00237] LCMS (ESI+): m/z 403.7 (M+H)⁺, RT: 1.597 min (Method A)

[00238] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.23 (s, 1 H) 7.92 (s, 1 H)

[00239] Synthesis of 6-bromo-3-iodo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00240] To a solution of 6,8-dibromo-3-iodo-imidazo[1,2-a]pyrazine (500 mg, 1.24 mmol, 1 eq) in THF (5 mL) was added (2S)-2-methylazetidine (267.08 mg, 2.48 mmol, 2 eq, HCl) and K₂CO₃ (686.20 mg, 4.97 mmol, 4 eq). The

mixture was exchanged with N₂ three times and was stirred at 60°C for 12 h under N₂ protection. TLC and LCMS showed all starting material was consumed and a new product was formed. The reaction mixture was quenched with H₂O (10 mL) and then extracted with ethyl acetate (10 mL × 3). The organic layers were combined and concentrated under reduced pressure to give 6-bromo-3-iodo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (450 mg, 92%) which was used without further purification.

[00241] LCMS (ESI+): m/z 392.9 (M+H)⁺, RT: 2.201 min (Method A)

[00242] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.54 (s, 1 H) 7.48 (s, 1 H) 4.76 - 5.11 (m, 1 H) 4.25 - 4.74 (m, 2 H) 2.48 - 2.79 (m, 1 H) 2.00 - 2.12 (m, 1 H) 1.65 (d, J=6.24 Hz, 3 H)

[00243] Synthesis of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine

[00244] A solution of 6-bromo-3-iodo-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (450 mg, 1.14 mmol, 1 eq) in DMF (9 mL) was added methyl 2,2-difluoro-2-fluorosulfonyl-acetate (791.88 mg, 4.12 mmol, 524.42 μL, 3.6 eq) and CuI (785.02 mg, 4.12 mmol, 3.6 eq). The mixture was degassed and purged with N₂ three times, and then stirred at 80°C for 8 h under N₂ atmosphere. LCMS showed the reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched by addition of H₂O (10 mL), and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 1/1) to give 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (250 mg, 65%).

[00245] LCMS (ESI+): m/z 335.0 (M+H)⁺, RT: 2.310 min (Method A)

[00246] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.77 (s, 1 H) 7.53 (s, 1 H) 4.17 - 5.17 (m, 3 H) 2.55 - 2.79 (m, 1 H) 1.98 - 2.20 (m, 1 H) 1.66 (br d, J=6.08 Hz, 3 H)

[00247] Synthesis of tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00248] To a solution of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (350 mg, 1.04 mmol, 1 eq) in a mixture of dioxane (3.6 mL) and H₂O (0.3 mL) was added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (437.68 mg, 1.25 mmol, 1.2 eq) and then K₂CO₃ (288.68 mg, 2.09 mmol, 2 eq). The resulting mixture was degassed and then was added DTBPF PdCl₂ (68.07 mg, 104.44 μmol, 0.1 eq). The mixture was exchanged with N₂ three times and was stirred at 80°C for 12 h under N₂ protection. TLC and LCMS showed all starting material was consumed and desired compound was detected. The reaction mixture was quenched with H₂O (10 mL) and then extracted with ethyl acetate (10 mL × 3). The organic layers were combined and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 80×30mm×3μm; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 50%-80% B over 8.0 min) to give tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (160 mg, 32%).

[00249] LCMS (ESI+): m/z 478.2 (M+H)⁺, RT: 2.379 min (Method A)

[00250] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine

[00251] A solution of tert-butyl 3-[4-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (150 mg, 314.15 μmol , 1 eq) in a mixture of DCM (1.25 mL) and TFA (0.25 mL) was stirred at 25°C for 2 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction was concentrated under reduced pressure to give the crude product 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (100 mg) which was used in the next step without further purification.

[00252] LCMS (ESI+): m/z 378.1 (M+H)⁺, RT: 1.772 min (Method A)

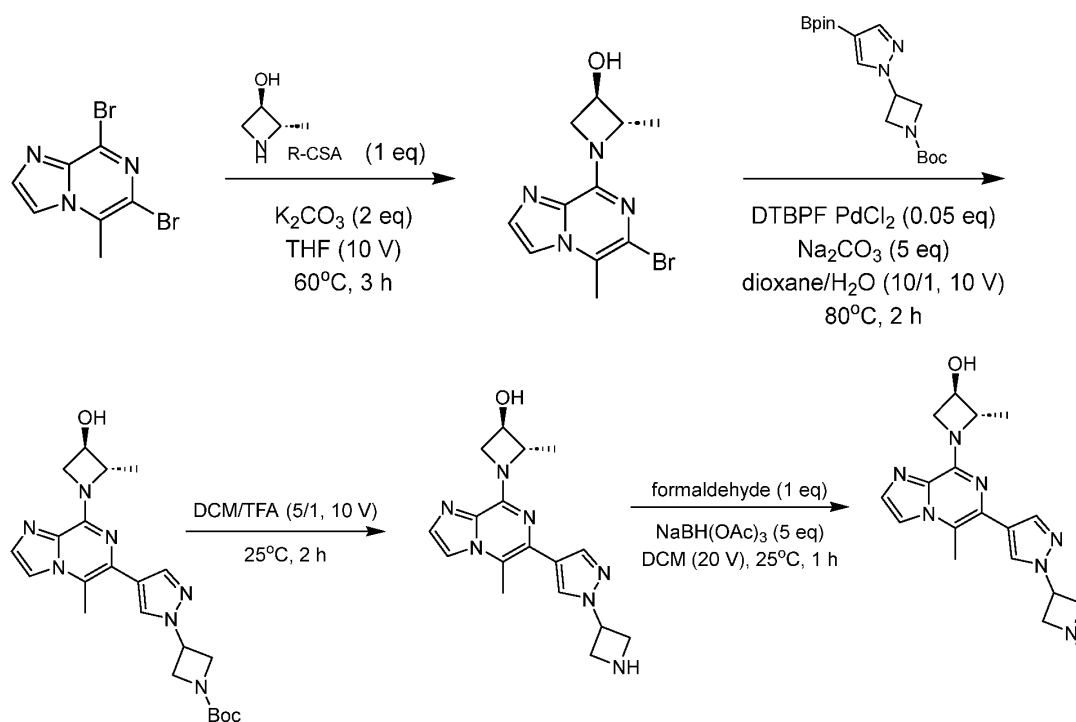
[00253] Synthesis of 8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine

[00254] To solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (100 mg, 264.99 μmol , 1 eq) in DCM (2 mL) was added formaldehyde (43.01 mg, 529.99 μmol , 39.46 μL , 37% purity, 2 eq) and NaBH(OAc)₃ (112.33 mg, 529.99 μmol , 2 eq). The reaction was stirred at 25°C for 1 h. LCMS showed starting material was consumed completely and one main peak with desired mass. The reaction mixture was purified by prep-HPLC, column: Phenomenex Luna C18 75×30mm×3 μm ; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 20%-50% B over 8.0 min to give 8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (90 mg, 87%).

[00255] LCMS (ESI+): m/z 392.1 (M+H)⁺, RT: 2.135 min (Method E)

[00256] ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.15 (d, J = 10.97 Hz, 2 H) 7.74 - 7.98 (m, 2 H) 5.42 (br s, 1 H) 4.88 - 4.99 (m, 2 H) 4.37 - 4.78 (m, 5 H) 3.00 - 3.23 (m, 3 H) 2.57 - 2.72 (m, 1 H) 2.06 - 2.19 (m, 1 H) 1.67 (d, J = 6.20 Hz, 3 H)

EXAMPLE 5: Synthesis of Compound A5



[00257] Synthesis of (2S, 3R)-1-(6-bromo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol

[00258] To a mixture of (2S,3R)-2-methylazetidin-3-ol (224.58 mg, 2.58 mmol, 1 eq, R-CSA salt) and 6,8-dibromo-5-methyl-imidazo[1,2-a]pyrazine (CAS# 909907-19-3; 250 mg, 859.28 μ mol, 1 eq) in THF (3 mL) was added K_2CO_3 (237.51 mg, 1.72 mmol, 2 eq). The mixture was stirred at 60°C for 3 h. LCMS showed the starting material was consumed completely and one main peak with desired mass. The reaction mixture was quenched by addition of water (5 mL) and extracted with ethyl acetate (8 mL $\times$ 3). The combined organic layers were washed with brine (7 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give (2S,3R)-1-(6-bromo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (225 mg, 88%) which was used in the next step directly.

[00259] LCMS (ESI+): m/z 297.0 (M+H)⁺, RT: 0.388 min (Method D)

[00260] 1H NMR (400 MHz, DMSO, 294 K) δ (ppm) = 7.94 (d, J = 0.8 Hz, 1H), 7.62 (d, J = 0.8 Hz, 1H), 5.69 (d, J = 6.4 Hz, 1H), 4.65 - 4.50 (m, 1H), 4.42 - 4.29 (m, 1H), 4.19 - 4.05 (m, 1H), 3.91 (br d, J = 4.9 Hz, 1H), 2.53 (s, 3H), 1.52 (d, J = 6.3 Hz, 3H)

[00261] Synthesis of tert-butyl 3-[4-[8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]-5-methyl-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00262] A mixture of tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (264.44 mg, 757.19 μ mol, 1 eq), (2S,3R)-1-(6-bromo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (225 mg, 757.19 μ mol, 1 eq), DTBPF $PdCl_2$ (24.67 mg, 37.86 μ mol, 0.05 eq), Na_2CO_3 (401.27 mg, 3.79 mmol, 5 eq) in dioxane (3 mL) and H_2O (0.3 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at

80°C for 2 hours under a N₂ atmosphere. LCMS showed the starting material was consumed completely and one main peak with desired mass. The reaction mixture was quenched by addition of water (5 mL), and extracted with ethyl acetate (8 mL × 3). The combined organic layers were washed with brine (7 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1:3, R_f = 0.5) to give tert-butyl 3-[4-[8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]-5-methyl-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (150 mg, 45%).

[00263] LCMS (ESI+): m/z 440.2 (M+H)⁺, RT: 0.374 min (Method D)

[00264] ¹H NMR (400 MHz, DMSO, 299 K) δ (ppm) = 8.14 (s, 1H), 7.93 (d, J = 1.0 Hz, 1H), 7.90 (s, 1H), 7.60 (d, J = 0.9 Hz, 1H), 5.59 (d, J = 6.6 Hz, 1H), 5.30 (tt, J = 5.4, 7.9 Hz, 1H), 4.63 - 4.55 (m, 1H), 4.35 - 4.28 (m, 3H), 4.20 (br s, 2H), 4.16 - 4.09 (m, 1H), 3.92 (dd, J = 5.3, 9.4 Hz, 1H), 2.57 (s, 3H), 1.56 (d, J = 6.4 Hz, 3H), 1.42 (s, 9H)

[00265] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00266] A solution of tert-butyl 3-[4-[8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]-5-methyl-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (150 mg, 341.29 μmol, 1 eq) in DCM (2 mL) and TFA (0.4 mL) was stirred at 25°C for 2 h. LCMS showed the starting material was consumed completely and one main peak with desired mass. The reaction was concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (115 mg, 99%) which was used in the next step directly.

[00267] LCMS (ESI+): m/z 340.3 (M+H)⁺, RT: 0.594 min (Method A)

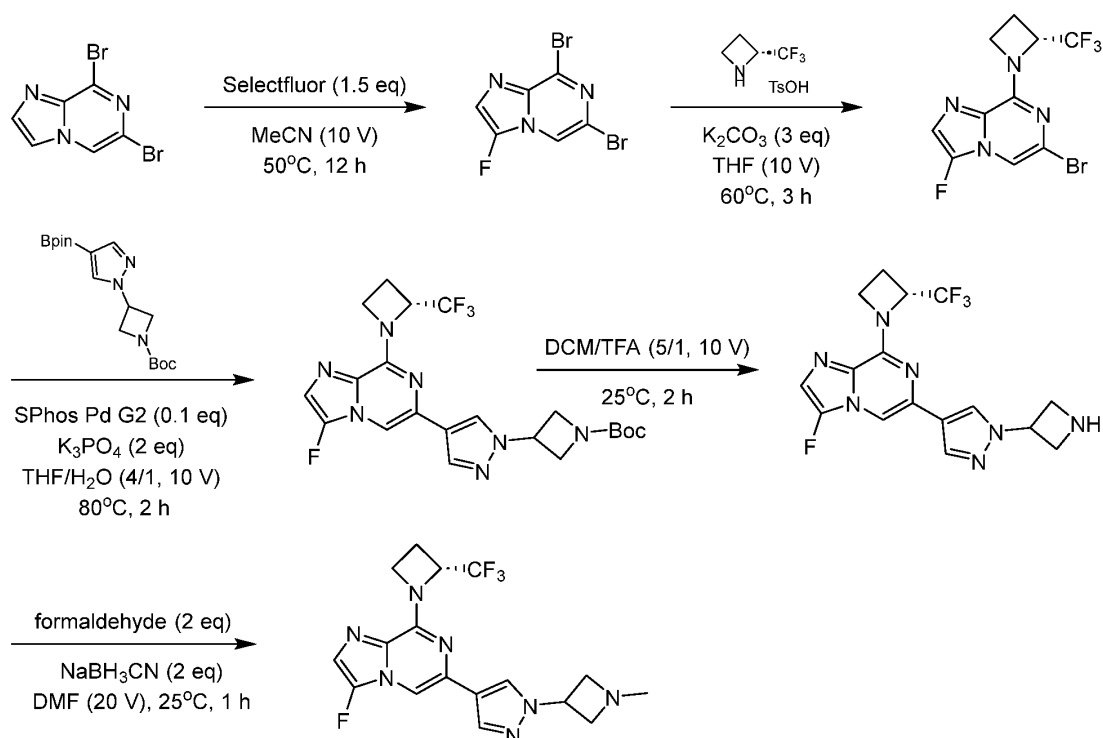
[00268] Synthesis of (2S,3R)-2-methyl-1-[5-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol

[00269] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (115 mg, 338.84 μmol, 1 eq) in DCM (2 mL) was added NaBH(OAc)₃ (359.07 mg, 1.69 mmol, 5 eq) and formaldehyde (27.50 mg, 338.84 μmol, 25.23 μL, 37% purity, 1 eq). The mixture was stirred at 25°C for 1 h. LCMS showed the starting material was consumed completely and one main peak with desired mass. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H₂O(10mM NH₄HCO₃)-ACN]; gradient: 20% - 50% B over 8.0 min) to give (2S,3R)-2-methyl-1-[5-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol (46 mg, 66%).

[00270] LCMS (ESI+): m/z 354.1 (M+H)⁺, RT: 2.108 min (Method F)

[00271] ¹H NMR (400 MHz, CD₃OD, 298 K) δ (ppm) = 8.05 (s, 1H), 7.90 (s, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.60 (d, J = 1.1 Hz, 1H), 5.11 (quin, J = 7.0 Hz, 1H), 4.82 - 4.74 (m, 1H), 4.52 - 4.43 (m, 1H), 4.28 - 4.21 (m, 1H), 4.03 - 3.97 (m, 1H), 3.96 - 3.90 (m, 2H), 3.72 (t, J = 7.6 Hz, 2H), 2.62 (s, 3H), 2.53 (s, 3H), 1.60 (d, J = 6.3 Hz, 3H)

EXAMPLE 6: Synthesis of Compound A6



[00272] Synthesis of 6,8-dibromo-3-fluoro-imidazo[1,2-a]pyrazine

[00273] To a solution of 6,8-dibromoimidazo[1,2-a]pyrazine (10 g, 36.11 mmol, 1 eq) in MeCN (100 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (19.19 g, 54.17 mmol, 1.5 eq). The mixture was stirred at 50°C for 12 h. TLC and LCMS showed all starting material was consumed and a new product formed. The reaction mixture was quenched by addition of water (100 mL). The mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC column: Welch Xtimate C18 250*100mm*10um; mobile phase: ([H₂O(10mM NH₄HCO₃)-ACN]; gradient: 20%-55% B over 18.0 min) to give 6,8-dibromo-3-fluoro-imidazo[1,2-a]pyrazine (2.4 g, 22%).

[00274] LCMS (ESI+): m/z 295.9 (M+H)⁺, RT: 1.959 min (Method J)

[00275] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.09 (s, 1 H) 7.49 (d, J=7.03 Hz, 1 H)

[00276] Synthesis of 6-bromo-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00277] To a solution of 6,8-dibromo-3-fluoro-imidazo[1,2-a]pyrazine (0.5 g, 1.70 mmol, 1 eq) in THF (5 mL) was added K₂CO₃ (702.99 mg, 5.09 mmol, 3 eq) and (2R)-2-(trifluoromethyl)azetidine (CAS # 2554776-09-7; 504.97 mg, 1.70 mmol, 1 eq, TsOH salt). The mixture was stirred at 60°C for 3 h. TLC and LCMS showed all starting material was consumed and a new product formed. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum

ether:ethyl acetate = 1:1, R_f = 0.4) to give 6-bromo-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.5 g, 87%).

[00278] LCMS (ESI+): m/z 339.0 (M+H)⁺, RT: 0.630 min (Method C)

[00279] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.50 (s, 1 H) 7.14 (d, J =7.09 Hz, 1 H) 5.22 (dt, J =9.14, 5.82 Hz, 1 H) 4.75 (td, J =8.86, 6.60 Hz, 1 H) 4.57 (td, J =9.35, 5.87 Hz, 1 H) 2.67 - 2.80 (m, 1 H) 2.54 - 2.65 (m, 1 H)

[00280] Synthesis of tert-butyl 3-[4-[3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00281] To a solution of 6-bromo-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.23 g, 678.29 μ mol, 1 eq) in THF (2 mL) and H₂O (0.5 mL) was added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (236.88 mg, 678.29 μ mol, 1 eq), K₃PO₄ (287.96 mg, 1.36 mmol, 2 eq) and chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (48.88 mg, 67.83 μ mol, 0.1 eq). The mixture was stirred at 80°C for 2 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL×3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:3, R_f = 0.4) to give tert-butyl 3-[4-[3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (0.2 g, 61%).

[00282] LCMS (ESI+): m/z 482.2 (M+H)⁺, RT: 2.838 min (Method F)

[00283] ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.92 (br t, J =4.05 Hz, 2 H) 7.48 - 7.56 (m, 1 H) 7.14 (br dd, J =7.03, 4.05 Hz, 1 H) 5.14 - 5.29 (m, 1 H) 4.97 - 5.13 (m, 2 H) 4.68 - 4.81 (m, 1 H) 4.52 - 4.66 (m, 1 H) 4.38 (br d, J =3.58 Hz, 3 H) 2.58 - 2.75 (m, 2 H) 1.47 (br d, J =5.01 Hz, 9 H)

[00284] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00285] A solution of tert-butyl 3-[4-[3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (0.2 g, 415.42 μ mol, 1 eq) in DCM (2 mL) and TFA (0.4 mL) was stirred at 25°C for 1 h. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to give 6-[1-(azetidine-3-yl)pyrazol-4-yl]-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidine-1-yl]imidazo[1,2-a]pyrazine (130 mg, 82%) which was used directly without further purification.

[00286] LCMS (ESI+): m/z 382.2 (M+H)⁺, RT: 0.364 min (Method D)

[00287] Synthesis of 3-fluoro-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00288] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-fluoro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.13 g, 340.91 μ mol, 1 eq) in DCM (3 mL) was added formaldehyde (55.33 mg, 681.82 μ mol, 50.76 μ L, 37%

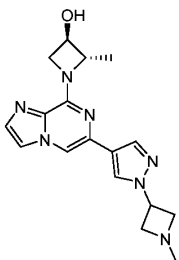
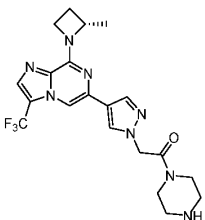
purity, 2 eq) and sodium cyanoborohydride (42.85 mg, 681.82 μ mol, 2 eq). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: ([H₂O(10mM NH₄HCO₃)-ACN]; gradient: 35%-65% B over 8.0 min) to give 3-fluoro-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (100 mg, 74%).

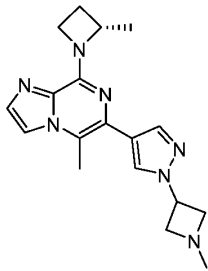
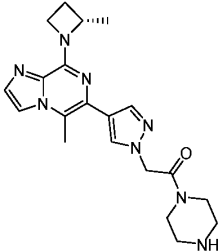
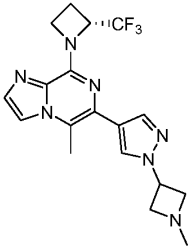
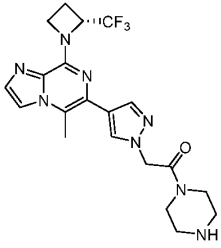
[00289] LCMS (ESI+): m/z 396.1 (M+H)⁺, RT: 2.678 min (Method F)

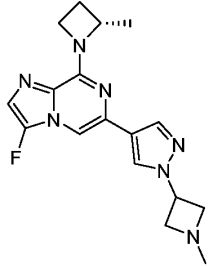
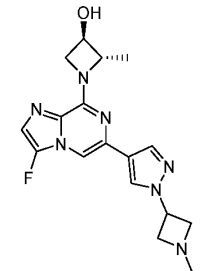
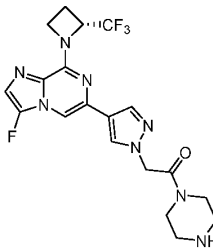
[00290] ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 8.15 (s, 1 H) 8.00 (s, 1 H) 7.93 (s, 1 H) 7.20 (d, J=6.97 Hz, 1 H) 5.27 (dqin, J=9.11, 6.31, 6.31, 6.31 Hz, 1 H) 5.04 (quin, J=7.09 Hz, 1 H) 4.65 (td, J=8.65, 5.69 Hz, 1 H) 4.46 - 4.56 (m, 1 H) 3.83 - 3.92 (m, 2 H) 3.58 - 3.67 (m, 2 H) 2.66 - 2.76 (m, 1 H) 2.60 (ddt, J=12.03, 8.73, 6.25, 6.25 Hz, 1 H) 2.49 (s, 3 H)

[00291] The compounds in Table C were made using similar methods as described for Examples A1-A6:

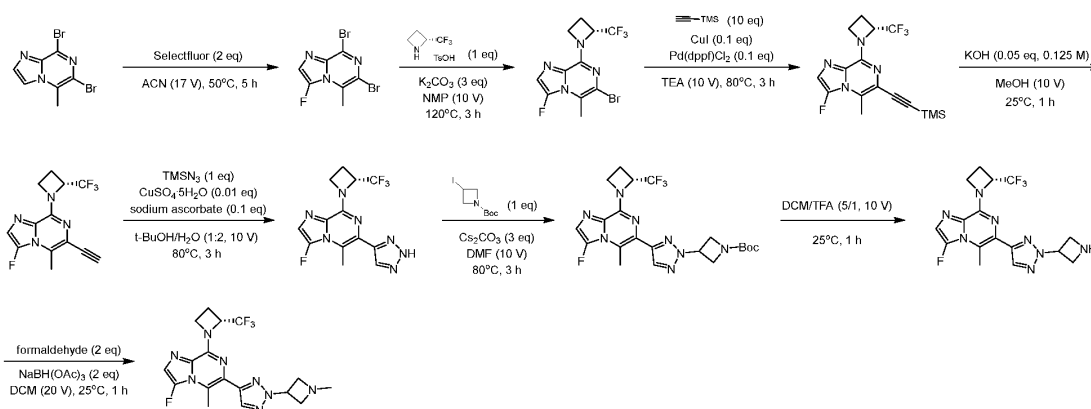
TABLE C

Compound number	Structure	MW	LCMS	¹ H NMR
A7		339.40	m/z 340.2 (M+H) ⁺ , RT: 1.963 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 8.13 (s, 1 H) 8.06 (s, 1 H) 7.95 (s, 1 H) 7.74 (s, 1 H) 7.51 (s, 1 H) 5.02 - 5.10 (m, 1 H) 4.50 - 4.58 (m, 2 H) 4.25 (br d, J=4.50 Hz, 1 H) 4.08 (br dd, J=9.57, 5.07 Hz, 1 H) 3.87 (br t, J=7.88 Hz, 2 H) 3.57 - 3.69 (m, 2 H) 2.49 (s, 3 H) 1.64 (br d, J=6.38 Hz, 3 H)
A8		448.45	m/z 449.1 (M+H) ⁺ , RT: 2.664 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ ppm 8.10 (s, 1 H) 7.97 (s, 1 H) 7.88 (s, 1 H) 7.84 (s, 1 H) 5.19 (s, 2 H) 4.89 - 4.96 (m, 1 H) 4.53 - 4.63 (m, 1 H) 4.37 - 4.48 (m, 1 H) 3.56 - 3.61 (m, 4 H) 2.86 - 2.90 (m, 2 H) 2.80 - 2.85 (m, 2 H) 2.58 - 2.69 (m, 1 H) 2.04 - 2.18 (m, 1 H) 1.67 (d, J=6.11 Hz, 3 H)

A9		337.43	m/z 338.2 (M+H) ⁺ , RT: 5.655 min (Method E)	1H NMR (400 MHz, METHANOL-d ₄) δ ppm 8.04 (s, 1 H) 7.87 (s, 1 H) 7.77 (s, 1 H) 7.57 (s, 1 H) 5.08 (t, J=7.15 Hz, 1 H) 4.79 - 4.87 (m, 1 H) 4.53 (td, J=8.76, 5.48 Hz, 1 H) 4.21 - 4.35 (m, 1 H) 3.82 - 3.99 (m, 2 H) 3.56 - 3.74 (m, 2 H) 2.59 (s, 3 H) 2.49 (m, 4 H) 1.97 - 2.13 (m, 1 H) 1.58 (d, J=6.08 Hz, 3 H)
A10		394.48	m/z 395.1 (M+H) ⁺ , RT: 2.190 min (Method F)	1H NMR (400 MHz, METHANOL-d ₄) δ ppm 7.93 (s, 1 H) 7.84 (s, 1 H) 7.75 (d, J=1.07 Hz, 1 H) 7.55 (d, J=1.07 Hz, 1 H) 5.20 (s, 2 H) 4.77 - 4.85 (m, 1 H) 4.52 (td, J=8.85, 5.19 Hz, 1 H) 4.21 - 4.31 (m, 1 H) 3.53 - 3.65 (m, 4 H) 2.88 - 2.95 (m, 2 H) 2.81 - 2.86 (m, 2 H) 2.59 (s, 3 H) 2.49 - 2.57 (m, 1 H) 2.07 (ddt, J=10.73, 9.00, 6.65, 6.65 Hz, 1 H) 1.58 (d, J=6.20 Hz, 3 H)
A11		391.40	m/z 392.2 (M+1) ⁺ , RT: 1.75 min (Method E)	1H NMR (400 MHz, METHANOL-d ₄) δ ppm 8.10 (s, 1 H) 8.08 (s, 1 H) 8.01 (d, J=1.34 Hz, 1 H) 7.79 (d, J=1.34 Hz, 1 H) 5.42 - 5.51 (m, 1 H) 5.31 (dt, J=9.02, 6.43 Hz, 1 H) 4.89 - 4.95 (m, 1 H) 4.70 (td, J=8.44, 5.62 Hz, 2 H) 4.46 - 4.62 (m, 2 H) 4.36 - 4.44 (m, 1 H) 3.02 - 3.22 (m, 3 H) 2.71 (s, 3 H) 2.60 - 2.70 (m, 2 H)
A12		448.45	m/z 449.0 (M+H) ⁺ , RT: 2.316 min (Method F)	1H NMR (400 MHz, METHANOL-d ₄) δ ppm 7.99 (s, 1 H) 7.91 (s, 1 H) 7.88 (d, J=1.19 Hz, 1 H) 7.64 (d, J=1.07 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 5.22 (s, 2 H) 4.66 (td, J=8.46, 5.60 Hz, 1 H) 4.34 - 4.44 (m, 1 H)

				3.56 - 3.62 (m, 4 H) 2.80 - 2.91 (m, 4 H) 2.69 (s, 3 H) 2.55 - 2.68 (m, 2 H)
A13		341.39	m/z 342.1 (M+H)+, RT: 2.602 min (Method E)	1H NMR (400 MHz, CHLOROFORM-d) δ = 8.15 (s, 1 H) 7.97 (s, 1 H) 7.73 (s, 1 H) 7.12 (d, J=6.97 Hz, 1 H) 5.05 (quin, J=7.09 Hz, 1 H) 4.86 - 4.94 (m, 1 H) 4.53 (td, J=9.08, 5.44 Hz, 1 H) 4.37 (td, J=9.20, 6.79 Hz, 1 H) 3.79 - 3.98 (m, 2 H) 3.57 - 3.69 (m, 2 H) 2.53 - 2.69 (m, 1 H) 2.49 (s, 3 H) 2.00 - 2.18 (m, 1 H) 1.64 (d, J=6.24 Hz, 3 H)
A14		357.39	m/z 358.1 (M+H)+, RT: 2.182 min (Method E)	1H NMR (400 MHz, METHANOL-d4) δ ppm 8.14 (s, 1 H) 7.97 (s, 1 H) 7.75 (s, 1 H) 7.13 (d, J=6.97 Hz, 1 H) 5.06 (quin, J=7.12 Hz, 1 H) 4.76 (dd, J=9.23, 7.03 Hz, 1 H) 4.52 (quin, J=5.75 Hz, 1 H) 4.21 - 4.29 (m, 1 H) 4.09 (dd, J=9.84, 4.83 Hz, 1 H) 3.87 - 3.95 (m, 2 H) 3.63 - 3.72 (m, 2 H) 2.51 (s, 3 H) 1.64 (d, J=6.48 Hz, 3 H)
A15		452.42	m/z 453.1 (M+H)+, RT: 2.403 min (Method F)	1H NMR (400 MHz, METHANOL-d4) δ ppm 8.04 (s, 1 H) 7.96 (s, 1 H) 7.92 (s, 1 H) 7.20 (d, J=6.97 Hz, 1 H) 5.21 - 5.31 (m, 1 H) 5.17 (s, 2 H) 4.59 - 4.70 (m, 1 H) 4.45 - 4.55 (m, 1 H) 3.57 (br s, 4 H) 2.77 - 2.95 (m, 4 H) 2.65 - 2.76 (m, 1 H) 2.53 - 2.64 (m, 1 H)

EXAMPLE 7: Synthesis of Compound A16



[00292] Synthesis of 6,8-dibromo-3-fluoro-5-methyl-imidazo[1,2-a]pyrazine

[00293] To a solution of 6,8-dibromo-5-methyl-imidazo[1,2-a]pyrazine (3 g, 10.31 mmol, 1 eq) in acetonitrile (50 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane; ditetrafluoroborate (7.31 g, 20.62 mmol, 2 eq). The mixture was stirred at 50°C for 5 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (200 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column on silica gel, eluted with petroleum ether:ethyl acetate = 1:0 to 3:1, (TLC: petroleum ether:ethyl acetate = 3:1, R_f=0.55) to give 6,8-dibromo-3-fluoro-5-methyl-imidazo[1,2-a]pyrazine (800 mg, 25% yield) as a white solid.

[00294] LCMS (ESI+): m/z 309.9 (M+H)⁺, RT: 0.536 min (Method C)

[00295] ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.46 (d, J=6.88 Hz, 1 H) 2.86 (d, J=4.88 Hz, 3 H).

[00296] Synthesis of 6-bromo-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00297] To a solution of 6,8-dibromo-3-fluoro-5-methyl-imidazo[1,2-a]pyrazine (0.75 g, 2.43 mmol, 1 eq) in NMP (8 mL) was added K₂CO₃ (1.01 g, 7.28 mmol, 3 eq) and (2R)-2-(trifluoromethyl)azetidine (723.07 mg, 2.43 mmol, 1 eq, TsOH salt). The mixture was stirred at 120°C for 3 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (10 mL). The mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 6-bromo-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.52 g, 61% yield) as a white solid which was used in the next reaction without purification.

[00298] LCMS (ESI+): m/z 352.9 (M+H)⁺, RT: 0.569 min (Method C)

[00299] Synthesis of 2-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]ethynyl-trimethyl-silane

[00300] To a solution of 6-bromo-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.52 g, 1.47 mmol, 1 eq) in TEA (5 mL) was added ethynyl(trimethyl)silane (1.45 g, 14.73 mmol, 2.04 mL, 10 eq), Pd(dppf)Cl₂ (107.75 mg, 147.26 μmol, 0.1 eq) and CuI (28.05 mg, 147.26 μmol, 0.1 eq). The mixture was stirred at 80°C for 3 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (10 mL). The mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 3:1, R_f=0.5) to give 2-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]ethynyl-trimethyl-silane (0.3 g, 55% yield) as a white solid.

[00301] LCMS (ESI+): m/z 371.1 (M+H)⁺, RT: 0.808 min (Method C)

[00302] Synthesis of 6-ethynyl-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00303] To a solution of 2-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]ethynyl-trimethyl-silane (0.3 g, 809.89 μmol, 1 eq) in MeOH (3 mL) was added aqueous solution of KOH (2.27 mg, 40.49 μmol, 0.05 eq, 0.125 M). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 6-ethynyl-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.215 g, 89% yield) as a white solid which was used in the next reaction without purification.

[00304] LCMS (ESI+): m/z 299.1 (M+H)⁺, RT: 0.656 min (Method C)

[00305] Synthesis of 3-fluoro-5-methyl-6-(2H-triazol-4-yl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00306] To a solution of 6-ethynyl-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.215 g, 720.90 μmol, 1 eq) in t-BuOH (0.75 mL) and H₂O (1.5 mL) was added TMSN₃ (83.05 mg, 720.90 μmol, 94.81 μL, 1 eq), CuSO₄·5H₂O (1.80 mg, 7.21 μmol, 0.01 eq) and sodium (2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-5-oxo-2H-furan-3-olate (14.28 mg, 72.09 μmol, 0.1 eq). The mixture was stirred at 80°C for 3 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL × 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 3-fluoro-5-methyl-6-(2H-triazol-4-yl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.135 g, 55% yield) as a white solid which was used in the next reaction without purification.

[00307] LCMS (ESI+): m/z 342.1 (M+H)⁺, RT: 0.580 min (Method C)

[00308] Synthesis of tert-butyl 3-[4-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]triazol-2-yl]azetidine-1-carboxylate

[00309] To a solution of 3-fluoro-5-methyl-6-(2H-triazol-4-yl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.135 g, 395.59 μ mol, 1 eq) in DMF (1.5 mL) was added tert-butyl 3-iodoazetidine-1-carboxylate (111.99 mg, 395.59 μ mol, 1 eq) and Cs_2CO_3 (386.67 mg, 1.19 mmol, 3 eq). The mixture was stirred at 80°C for 3 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2 , petroleum ether: ethyl acetate = 3:1, R_f =0.55) to give tert-butyl 3-[4-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]triazol-2-yl]azetidine-1-carboxylate (0.1 g, 51% yield) as a white solid.

[00310] LCMS (ESI+): m/z 497.2 (M+H)⁺, RT: 0.770 min (Method C)

[00311] ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.12 (s, 1 H) 7.19 (d, J =6.97 Hz, 1 H) 5.39 - 5.48 (m, 1 H) 5.09 - 5.19 (m, 1 H) 4.67 - 4.76 (m, 1 H) 4.44 - 4.55 (m, 5 H) 3.01 (d, J =5.75 Hz, 3 H) 2.64 (q, J =7.50 Hz, 2 H) 1.49 (s, 9 H).

[00312] Synthesis of 6-[2-(azetidin-3-yl)triazol-4-yl]-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00313] To a solution of tert-butyl 3-[4-[3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]triazol-2-yl]azetidine-1-carboxylate (0.1 g, 201.43 μ mol, 1 eq) in DCM (1 mL) was added TFA (0.2 mL). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give 6-[2-(azetidin-3-yl)triazol-4-yl]-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.065 g, 164.00 μ mol, 81.42% yield) as white solid which was used in the next reaction without purification.

[00314] LCMS (ESI+): m/z 397.1 (M+H)⁺, RT: 0.533 min (Method C)

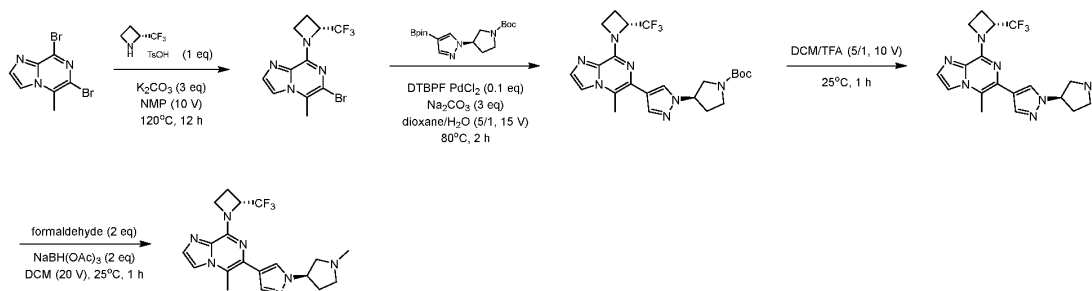
[00315] Synthesis of 3-fluoro-5-methyl-6-[2-(1-methylazetidin-3-yl)triazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00316] To a solution of 6-[2-(azetidin-3-yl)triazol-4-yl]-3-fluoro-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.065 g, 164.00 μ mol, 1 eq) in DCM (1 mL) was added HCHO (26.62 mg, 328.00 μ mol, 24.42 μ L, 37% purity, 2 eq) and $\text{NaBH}(\text{OAc})_3$ (69.52 mg, 328.00 μ mol, 2 eq). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was purified by prep-HPLC, column: Waters Xbridge Prep OBD C18 150 $\times$ 40mm $\times$ 10 μ m; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient:40%-70% B over 8.0 min) to give 3-fluoro-5-methyl-6-[2-(1-methylazetidin-3-yl)triazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.03 g, 45% yield) as a white solid.

[00317] LCMS (ESI+): m/z 411.2 (M+H)⁺, RT: 2.048 min (Method E)

[00318] ^1H NMR (400 MHz, METHANOL-d_4) δ 8.08 (s, 1 H) 7.26 (d, J =6.85 Hz, 1 H) 5.34 (quin, J =6.97 Hz, 1 H) 5.17 - 5.27 (m, 1 H) 4.61 - 4.64 (m, 1 H) 4.41 - 4.50 (m, 1 H) 3.89 - 4.00 (m, 2 H) 3.78 (br t, J =7.27 Hz, 2 H) 3.02 (d, J =5.87 Hz, 3 H) 2.55 - 2.74 (m, 2 H) 2.50 (s, 3 H).

EXAMPLE 8: Synthesis of Compound A17

**[00319]** Synthesis of 6-bromo-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00320] To a solution of 6,8-dibromo-5-methyl-imidazo[1,2-a]pyrazine (300 mg, 1.03 mmol, 1 eq) in NMP (3 mL) was added K_2CO_3 (427.52 mg, 3.09 mmol, 3 eq) and (2R)-2-(trifluoromethyl)azetidine (306.54 mg, 1.03 mmol, 1 eq, TsOH salt). The mixture was stirred at 120°C for 12 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2 , petroleum ether:ethyl acetate = 3:1, R_f =0.55) to give 6-bromo-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (250 mg, 72% yield) as a white solid.

[00321] LCMS (ESI+): m/z 335.0 (M+H)⁺, RT: 0.641 min (Method C)

[00322] Synthesis of tert-butyl (3R)-3-[4-[5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidine-1-carboxylate

[00323] To a solution of 6-bromo-5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.25 g, 746.00 μ mol, 1 eq) in dioxane (3 mL) and H_2O (0.6 mL) was added tert-butyl (3R)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]pyrrolidine-1-carboxylate (CAS# 1175273-52-5; 325.19 mg, 895.19 μ mol, 1.2 eq), Na_2CO_3 (237.20 mg, 2.24 mmol, 3 eq) and di-tert-butyl(cyclopentyl)phosphane;dichloropalladium;iron (48.62 mg, 74.60 μ mol, 0.1 eq). The mixture was stirred at 80°C for 2 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (10 mL). The mixture was extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2 , petroleum ether:ethyl acetate = 2:1, R_f =0.5) to give tert-butyl (3R)-3-[4-[5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidine-1-carboxylate (0.3 g, 82% yield) as a white solid.

[00324] LCMS (ESI+): m/z 492.2 (M+H)⁺, RT: 0.487 min (Method D)

[00325] Synthesis of 5-methyl-6-[1-[(3R)-pyrrolidin-3-yl]pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00326] To a solution of tert-butyl (3R)-3-[4-[5-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidine-1-carboxylate (0.3 g, 610.37 μ mol, 1 eq) in DCM (3 mL) was added TFA (0.5 mL). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give 5-methyl-6-[1-[(3R)-pyrrolidin-3-yl]pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.2 g, 84% yield) as a white solid which was used in the next reaction without purification.

[00327] LCMS (ESI+): m/z 392.1 (M+H)⁺, RT: 0.330 min (Method D)

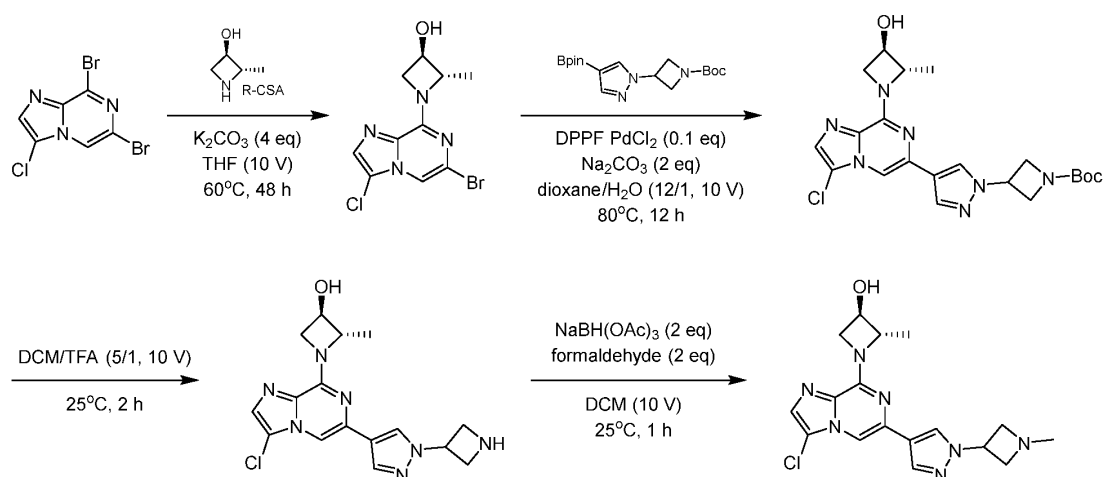
[00328] Synthesis of 5-methyl-6-[1-[(3R)-1-methylpyrrolidin-3-yl]pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00329] To a solution of 5-methyl-6-[1-[(3R)-pyrrolidin-3-yl]pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.1 g, 255.50 μ mol, 1 eq) in DCM (1 mL) was added HCHO (41.47 mg, 511.00 μ mol, 38.04 μ L, 37% purity, 2 eq) and NaBH(OAc)₃ (108.30 mg, 511.00 μ mol, 2 eq). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and one main peak with desired mass was detected. The reaction mixture was quenched by addition of water (5 mL). The mixture was extracted with ethyl acetate (3 mL $\times$ 3). The combined organic layers were washed with brine (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was suspended in heptane (2 mL) and stirred at 25°C for 0.5 h, then the residue was collected by filtration and dried to give 5-methyl-6-[1-[(3R)-1-methylpyrrolidin-3-yl]pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.07 g, 172.66 μ mol, 67.58% yield) as a white solid.

[00330] LCMS (ESI+): m/z 406.2 (M+H)⁺, RT: 1.777 min (Method F)

[00331] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.07 (s, 1 H) 7.86 (d, J=4.52 Hz, 2 H) 7.62 (s, 1 H) 5.17 - 5.32 (m, 1 H) 4.96 - 5.09 (m, 1 H) 4.59 - 4.72 (m, 1 H) 4.38 (q, J=8.35 Hz, 1 H) 3.08 (dd, J=9.84, 7.89 Hz, 1 H) 2.85 - 2.96 (m, 2 H) 2.56 - 2.77 (m, 5 H) 2.51 (br dd, J=15.22, 6.17 Hz, 1 H) 2.43 (s, 3 H) 2.20 - 2.32 (m, 1 H).

EXAMPLE 9: Synthesis of Compound A18



[00332] Synthesis of (2S,3R)-1-(6-bromo-3-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol

[00333] To a solution of 6,8-dibromo-3-chloro-imidazo[1,2-a]pyrazine (CAS# 1255097-94-9; 250 mg, 802.93 μ mol, 1 eq) and (2S,3R)-2-methylazetidin-3-ol (293.79 mg, 802.93 μ mol, 1.14 eq, R-CSA salt; synthesized as described in J. Med. Chem. 2020, 63, 13546–13560, intermediate 13/(R)-CSA salt) in THF (2.5 mL) was added with K_2CO_3 (443.88 mg, 3.21 mmol, 4 eq) at 20°C. The mixture was stirred at 60°C for 48 hrs. LCMS showed starting material was consumed completely and one new peak with desired mass was detected. After cooling to 20°C, the reaction mixture was concentrated under reduced pressure. The residue was triturated with water (20 mL), filtered, and the filter cake was dried by high vacuum to give (2S,3R)-1-(6-bromo-3-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (250 mg, yield 96.08%) as a white solid, which was used in the next step directly without purification.

[00334] LCMS (ESI+): m/z 317.0, 319.0 (M+H, M+3)+, RT: 0.407 min (Method N).

[00335] 1H NMR (400 MHz, CHLOROFORM-d) δ 7.50 (s, 1H), 7.41 (s, 1H), 4.82 (br dd, J=9.76, 6.88 Hz, 1 H), 4.65 (br d, J=4.50 Hz, 1 H), 4.31 - 4.38 (m, 1 H), 4.21 (br dd, J=10.69, 4.06 Hz, 1 H), 1.65 (d, J=6.50 Hz, 3 H)

[00336] Synthesis of tert-butyl 3-[4-[3-chloro-8-[(2S, 3R)-3-hydroxy-2-methyl-azetidin-1-yl]imidazo [1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00337] To a solution of (2S,3R)-1-(6-bromo-3-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (200 mg, 629.78 μ mol, 1 eq) and tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (263.93 mg, 755.74 μ mol, 1.2 eq) in dioxane (1.8 mL) and H_2O (0.2 mL) was added with $Pd(dppf)Cl_2$ (23.04 mg, 31.49 μ mol, 0.05 eq) and Na_2CO_3 (133.50 mg, 1.26 mmol, 2 eq) at 20°C under nitrogen. The mixture was stirred at 80°C for 12 hrs. LCMS showed starting material was consumed completely and one new peak with desired mass was detected. After cooling to 20°C, the residue was diluted with water (10 mL) and extracted with ethyl acetate (6 mL $\times$ 3). The combined organic layers were washed with brine (2 mL $\times$ 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 3:1 to 1:1 to give tert-butyl 3-[4-[3-chloro-8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (400 mg, yield 99.43%) as a yellow solid.

[00338] LCMS (ESI+): m/z 460 (M+H)+, RT: 0.428 min (Method N)

[00339] 1H NMR (400 MHz, DMSO-d₆) δ 8.36 (s, 1H), 8.11 (s, 1H), 8.00 (s, 1H), 7.65 (s, 1H), 5.68 (d, 1H, J = 6.63 Hz), 5.2-5.3 (m, 1H), 4.64 (br s, 1H), 4.4 (br s, 1H), 4.30 (br d, J=7.75 Hz, 2 H), 4.16 (br d, J=4.50 Hz, 3 H), 1.59 (br d, J=6.25 Hz, 3 H), 1.42 (s, 9 H)

[00340] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-chloro-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00341] To a solution of tert-butyl 3-[4-[3-chloro-8-[(2S,3R)-3-hydroxy-2-methyl-azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (400 mg, 869.70 μ mol, 1 eq) in DCM (3 mL) was added TFA (0.6 mL). The mixture was stirred at 25°C for 2 hrs. LCMS showed starting material was consumed completely and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent.

The residue was diluted with DCM (5 mL), neutralized by saturated aqueous NaHCO_3 to pH = 8, extracted with DCM (5 mL $\times$ 3). The combined organic phase was dried with Na_2SO_4 , filtered and concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-chloro-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (250 mg, yield 73.5%) as a white solid, which was directly used in the next step without purification.

[00342] LCMS (ESI+): m/z 360.1 (M+H)⁺, RT: 0.253 min (Method N)

[00343] ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.30 (s, 1 H), 8.23 (s, 1 H), 7.98 (s, 1 H), 7.64 (s, 1 H), 5.48 (quin, J=7.57 Hz, 1 H), 4.64 (br d, J=7.13 Hz, 1 H), 4.33 - 4.48 (m, 6 H), 4.13 - 4.19 (m, 1 H), 4.03 (br dd, J=9.88, 5.00 Hz, 1 H), 1.59 (d, J=6.38 Hz, 3 H)

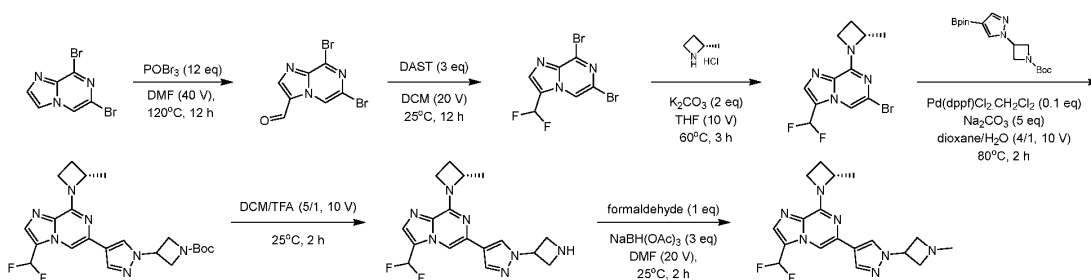
[00344] Synthesis of (2S,3R)-1-[3-chloro-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00345] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-chloro-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (250 mg, 694.81 μmol , 1 eq) in DCM (5 mL) was added formaldehyde (56.38 mg, 694.81 μmol , 51.73 μL , 1 eq) and $\text{NaBH}(\text{OAc})_3$ (441.77 mg, 2.08 mmol, 3 eq) at 20°C. The mixture was stirred at 25°C for 1 hr. LCMS showed starting material was consumed completely and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (neutral condition, column: CD02-Waters Xbridge BEH C18 150 $\times$ 25 $\times$ 10 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 10%-40% B over 10 min) to give (2S,3R)-1-[3-chloro-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (85 mg, yield 32.4%) as a white solid.

[00346] LCMS (ESI+): m/z 374.2 (M+H)⁺, RT: 1.663 min (Method O)

[00347] ^1H NMR (400 MHz, METHANOL- d_4) δ 8.20 (s, 1 H), 8.01 (s, 1 H), 7.84 (s, 1 H), 7.47 (s, 1 H), 5.06 (quin, J=7.10 Hz, 1 H), 4.78 (dd, J=9.63, 6.75 Hz, 1 H), 4.53 (quin, J=5.78 Hz, 1 H), 4.22 - 4.30 (m, 1 H), 4.10 (dd, J=9.76, 4.88 Hz, 1 H), 3.87 (t, J=8.07 Hz, 2 H), 3.64 (t, J=7.75 Hz, 2 H), 2.49 (s, 3 H), 1.65 (d, J=6.38 Hz, 3 H)

EXAMPLE 10: Synthesis of Compound A19



[00348] Synthesis of 6,8-dibromoimidazo[1,2-a]pyrazine-3-carbaldehyde

[00349] To a solution of 6,8-dibromoimidazo[1,2-a]pyrazine (1 g, 3.49 mmol, 1 eq) in DMF (40 mL) was added POBr_3 (11.59 g, 41.86 mmol, 12 eq). The mixture was stirred at 120°C for 12h. TLC (petroleum ether:ethyl acetate = 1:3, R_f = 0.3) showed all starting material was consumed and one new product generated. The reaction mixture was quenched

by addition of water (30 mL) at 25°C, and then extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1/5) to give 6,8-dibromoimidazo[1,2-a]pyrazine-3-carbaldehyde (700 mg, 64% yield) as a yellow solid.

[00350] ¹H NMR (400 MHz, DMSO-d₆) δ 10.12 (s, 1 H) 9.37 (s, 1 H) 8.69 (s, 1 H).

[00351] Synthesis of 6,8-dibromo-3-(difluoromethyl)imidazo[1,2-a]pyrazine

[00352] To a solution of 6,8-dibromoimidazo[1,2-a]pyrazine-3-carbaldehyde (700 mg, 2.3 mmol, 1 eq) in DCM (14 mL) was added DAST (255.43 mg, 6.89 mmol, 3 eq). The mixture was stirred at 25°C for 12h. LCMS indicated product with desired mass was detected. The reaction mixture was quenched by addition of water (20 mL) at 25°C, and then extracted with ethyl acetate (5 mL×3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1/5) to give 6,8-dibromo-3-(difluoromethyl)imidazo[1,2-a]pyrazine (2 g, 58% yield) as a yellow solid.

[00353] LCMS (ESI+): m/z 325.9 (M+1)+, RT: 0.473 min (Method C)

[00354] Synthesis of 6-bromo-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00355] To a solution of (2S)-2-methylazetidine (108.78 mg, 1.53 mmol, 1eq, HCl salt) and 6,8-dibromo-3-(difluoromethyl)imidazo[1,2-a]pyrazine (500 mg, 1.53 mmol, 1 eq) in THF (5 mL) was added K₂CO₃ (422.74 mg, 3.06 mmol, 2 eq). The mixture was stirred at 60°C for 3 h. TLC (petroleum ether:ethyl acetate = 1:1, R_f = 0.6) showed all starting material was consumed and one new product formed. The reaction mixture was quenched by addition of water (5 mL) at 25°C, and then extracted with ethyl acetate (2 mL × 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1/5) to give 6-bromo-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (385 mg, 79% yield) as a white solid.

[00356] ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (s, 1 H) 7.86 (s, 1 H) 7.49 (t, J=53.17 Hz, 1 H) 4.65 - 5.06 (m, 1 H) 4.06 - 4.59 (m, 2 H) 2.52 - 2.67 (m, 1 H) 1.92 - 2.07 (m, 1 H) 1.56 (br s, 3 H)

[00357] Synthesis of tert-butyl 3-[4-[3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00358] To a solution of tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (423.97 mg, 1.21 mmol, 1eq) and 6-bromo-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (385 mg, 1.21 mmol, 1 eq) in H₂O (1 mL) and dioxane (5 mL) was added Na₂CO₃ (643.34 mg, 6.07 mmol, 5 eq) and cyclopentyl(diphenyl)phosphane; dichloromethane; dichloropalladium; iron (99.1 mg, 0.121 mmol, 0.1 eq). The mixture was stirred at 80°C for 2h. TLC (petroleum ether:ethyl acetate = 1:1, R_f=0.3) showed all starting material was consumed and one new product generated. The reaction mixture was quenched by addition of water (5 mL) at 25°C, and then extracted with ethyl acetate (2 mL×3). The combined organic layers were washed with brine (3 mL), dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate = 1:1) to give tert-butyl 3-[4-[3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (280 mg, 50% yield) as a white solid.

[00359] ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (s, 1 H) 8.06 (d, J=11.68 Hz, 2 H) 7.82 - 7.90 (m, 1 H) 7.31 - 7.59 (m, 1 H) 5.21 - 5.33 (m, 1 H) 4.81 (br d, J=2.86 Hz, 1 H) 4.40 - 4.53 (m, 1 H) 4.22 - 4.32 (m, 3 H) 4.15 (br s, 2 H) 2.52 - 2.61 (m, 1 H) 2.00 - 2.09 (m, 1 H) 1.61 (d, J=6.20 Hz, 3 H) 1.41 (s, 9 H)

[00360] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00361] To a solution of tert-butyl 3-[4-[3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (280 mg, 609.36 μmol, 1 eq) in DCM (2 mL) was added TFA (0.4 mL). The mixture was stirred at 25°C for 2h. TLC (petroleum ether:ethyl acetate = 1:3, R_f=0.6) showed all starting material was consumed and one new product formed. The reaction mixture was quenched by addition of saturated sodium bicarbonate (5 mL) at 25°C, and then extracted with ethyl acetate (1 mL × 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (130 mg, 59% yield) as a yellow oil, which was used in the next reaction directly.

[00362] LCMS (ESI+): m/z 360.2 (M+1)⁺, RT: 0.403 min (Method C)

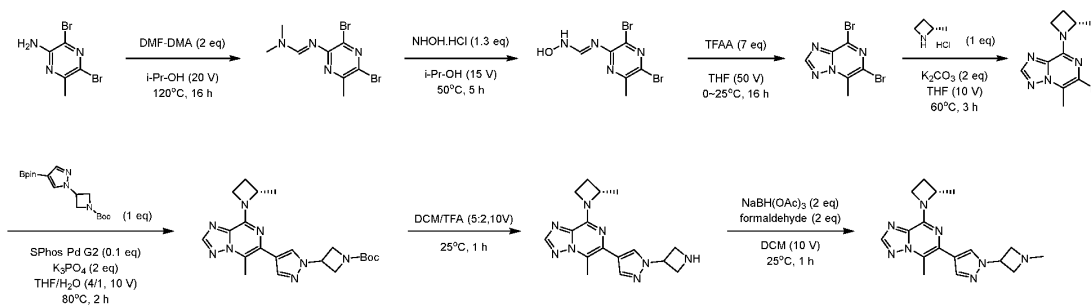
[00363] Synthesis of 3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine

[00364] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (130 mg, 361.73 μmol, 1 eq) in DMF (2 mL) was added formaldehyde (29.3 mg, 361.73 μmol, 37% purity, 1 eq) and NaBH(OAc)₃ (229.99 mg, 1.09 mmol, 3 eq). The mixture was stirred at 25°C for 2h. LCMS indicated product with desired mass was detected. The reaction mixture was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150×40mm×10μm; mobile phase: [H₂O(10mM NH₄HCO₃)-ACN]; gradient: 20%-70% B over 8.0 min to give 3-(difluoromethyl)-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine (40 mg, 30% yield) as a white solid.

[00365] LCMS (ESI+): m/z 374.1 (M+1)⁺, RT: 2.702 min (Method F)

[00366] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.19 (s, 1 H) 7.96 (d, J=11.86 Hz, 2 H) 7.73 (t, J=1.83 Hz, 1 H) 7.22 (t, J=53.25 Hz, 1 H) 5.06 (quin, J=7.06 Hz, 1 H) 4.89 - 4.96 (m, 1 H) 4.57 (td, J=9.14, 5.56 Hz, 1 H) 4.33 - 4.46 (m, 1 H) 3.84 - 3.93 (m, 2 H) 3.61 - 3.69 (m, 2 H) 2.56 - 2.67 (m, 1 H) 2.49 (s, 3 H) 2.10 (ddt, J=10.88, 9.08, 6.34, 6.34 Hz, 1 H) 1.65 (d, J=6.24 Hz, 3 H)

EXAMPLE 11: Synthesis of Compound A20



[00367] Synthesis of N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N,N-dimethyl-formamidine

[00368] To a solution of 3,5-dibromo-6-methyl-pyrazin-2-amine (3 g, 11.24 mmol, 1 eq) in i-PrOH (60 mL) was added DMF-DMA (2.68 g, 22.48 mmol, 2.99 mL, 2 eq). The mixture was stirred at 120°C for 6 hr. TLC indicated one new product formed. The reaction mixture was diluted with H₂O (60 mL) and extracted with EA (60 mL × 2). The combined organic layers were washed with aqueous NaCl (75 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE:EA = 2:1) to give N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N,N-dimethyl-formamidine (3 g, 83% yield) as a colourless oil.

[00369] Synthesis of N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N-hydroxy-formamidine

[00370] To a solution of N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N,N-dimethyl-formamidine (3 g, 9.32 mmol, 1 eq) in i-PrOH (45 mL) was added hydroxylamine hydrochloride (841.66 mg, 12.11 mmol, 1.3 eq). The mixture was stirred at 50°C for 5 hr. TLC indicated one new product formed. The reaction mixture was diluted with H₂O (60 mL) and extracted with EA (60 mL × 2). The combined organic layers were washed with aqueous NaCl (75 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N-hydroxy-formamidine (2.8 g, 97% yield) as a colourless oil.

[00371] Synthesis of 6,8-dibromo-5-methyl-[1,2,4]triazolo[1,5-a]pyrazine

[00372] To a solution of N'-(3,5-dibromo-6-methyl-pyrazin-2-yl)-N-hydroxy-formamidine (2.8 g, 9.03 mmol, 1 eq) in THF (140 mL) was added TFAA (13.28 g, 63.24 mmol, 8.79 mL, 7 eq). The mixture was stirred at 25°C for 16 hr. TLC indicated one new product formed. The reaction mixture was diluted with H₂O (150 mL) and extracted with EA (150 mL × 2). The combined organic layers were washed with aqueous NaCl (200 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE:EA = 2:1) to give 6,8-dibromo-5-methyl-[1,2,4]triazolo[1,5-a]pyrazine (2.5 g, 95% yield) as a yellow solid.

[00373] Synthesis of 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine

[00374] To a solution of 6,8-dibromo-5-methyl-[1,2,4]triazolo[1,5-a]pyrazine (0.3 g, 1.03 mmol, 1 eq) in THF (3 mL) was added K₂CO₃ (284.05 mg, 2.06 mmol, 2 eq) and (2S)-2-methylazetidine (110.56 mg, 1.03 mmol, 1 eq, HCl salt). The mixture was stirred at 60 °C for 3 hr. LCMS showed one main peak with desired mass was detected. The reaction mixture was diluted with H₂O (3 mL) and extracted with EA (3 mL × 2). The combined organic layers were washed with aqueous NaCl (6 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was

purified by prep-TLC (SiO₂, PE: EA = 2:1) to give 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (0.12 g, 41% yield) as a yellow solid.

[00375] LCMS (ESI+): m/z 282.1 (M+H)⁺, RT: 0.596 min (Method C)

[00376] ¹H NMR (400 MHz, DMSO-d₆) δ 1.58 (d, J=6.20 Hz, 3 H) 1.99 - 2.10 (m, 1 H) 2.34 (s, 1 H) 2.62 (s, 3 H) 4.06 - 4.44 (m, 2 H) 4.78 (br d, J=3.22 Hz, 1 H) 8.52 (s, 1 H)

[00377] Synthesis of tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00378] A mixture of 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (0.06 g, 212.66 μmol, 1 eq), K₃PO₄ (180.56 mg, 850.64 μmol, 4 eq) and [2-(2-aminophenyl)phenyl]-chloro-palladium dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (15.32 mg, 21.27 μmol, 0.1 eq) and tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (81.69 mg, 233.93 μmol, 1.1 eq) in a mixture of dioxane (5 mL) and water (1.2 mL) was degassed and purged with nitrogen three times, and then the mixture was stirred at 80°C for 2 h under nitrogen atmosphere. LCMS showed one main peak with desired mass was detected. The reaction mixture was diluted with H₂O 6 mL and extracted with EA (6 mL × 2). The combined organic layers were washed with aqueous NaCl (12 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, PE:EA = 2:1) to give tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (0.12 g, 66% yield) as a white solid.

[00379] LCMS (ESI+): m/z 435.3 (M+H)⁺, RT: 0.585 min (Method C)

[00380] ¹H NMR (400 MHz, DMSO-d₆) δ 1.42 (s, 9 H) 1.60 (d, J=6.20 Hz, 3 H) 2.02 - 2.12 (m, 1 H) 2.40 - 2.44 (m, 1 H) 2.71 (s, 3 H) 4.14 - 4.23 (m, 2 H) 4.24 - 4.39 (m, 4 H) 4.67 - 4.84 (m, 1 H) 5.23 - 5.39 (m, 1 H) 7.98 (s, 1 H) 8.23 (s, 1 H) 8.50 (s, 1 H)

[00381] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine

[00382] A solution of tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (0.11 g, 259.13 μmol, 1 eq) in DCM (1 mL) and TFA (0.4 mL) was stirred at 25 °C for 2 hr. LCMS showed one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (0.08 g, 95% yield) as a colourless oil, which was used directly in the next reaction.

[00383] LCMS (ESI+): m/z 325.3 (M+H)⁺, RT: 0.375 min (Method H)

[00384] Synthesis of 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazine

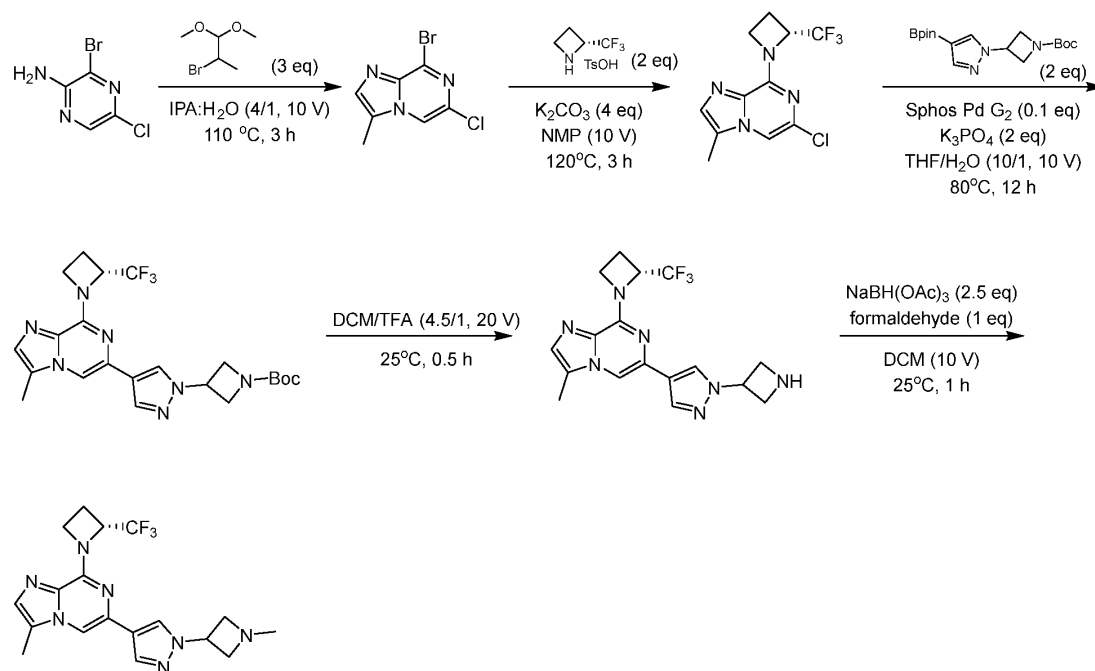
[00385] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (0.08 g, 246.62 μmol, 1 eq) in DCM (0.1 mL) was added NaBH(OAc)₃ (104.54 mg, 493.24 μmol, 2 eq) and

formaldehyde (40.03 mg, 493.24 μ mol, 36.72 μ L, 37% purity, 2 eq). The mixture was stirred at 25°C for 1 hr. LCMS showed one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Gemini NX-C18(75 $\times$ 30mm $\times$ 3 μ m); mobile phase: [H₂O(0.05% NH₃.H₂O+10mM NH₄HCO₃)-ACN]; gradient: 20%-50% B over 8.0 min) to give 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-[1,2,4]triazolo[1,5-a]pyrazine (0.03 g, 36% yield) as a white solid.

[00386] LCMS (ESI+): m/z 339.1 (M+H)⁺, RT: 2.504 min (Method F)

[00387] ¹H NMR (400 MHz, METHANOL-d₄) δ 1.64 (d, J=6.24 Hz, 3 H) 2.11 (ddt, J=10.84, 9.00, 6.59, 6.59 Hz, 1 H) 2.49 (s, 3 H) 2.60 (dtd, J=10.90, 8.73, 8.73, 5.26 Hz, 1 H) 2.75 (s, 3 H) 3.61 - 3.74 (m, 2 H) 3.83 - 3.95 (m, 2 H) 4.31 (td, J=9.02, 7.03 Hz, 1 H) 4.47 (td, J=8.96, 5.32 Hz, 1 H) 4.80 - 4.85 (m, 1 H) 5.09 (quin, J=7.12 Hz, 1 H) 7.95 (s, 1 H) 8.11 (s, 1 H) 8.33 (s, 1 H)

EXAMPLE 12: Synthesis of Compound A21



[00388] Synthesis of 8-bromo-6-chloro-3-methyl-imidazo[1,2-a]pyrazine

[00389] To a solution of 3-bromo-5-chloro-pyrazin-2-amine (1 g, 4.80 mmol, 1 eq) in IPA (8 mL) and H₂O (2 mL) was added 2-bromo-1,1-dimethoxy-propane (2.63 g, 14.39 mmol, 3 eq) at 110°C. The reaction was stirred at 110°C for 3 h. LCMS showed starting material was consumed and desired product was detected. The reaction was filtered and solid was dried to give 8-bromo-6-chloro-3-methyl-imidazo[1,2-a]pyrazine (0.65 g, 55% yield) as a white solid.

[00390] LCMS (ESI+): m/z 247.9 (M+1)⁺, RT: 0.371 min (Method D)

[00391] Synthesis of 6-chloro-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidine-1-yl]imidazo[1,2-a]pyrazine

[00392] To a solution of (2R)-2-(trifluoromethyl)azetidine (405.99 mg, 3.25 mmol, 2 eq) in NMP (4 mL) was added 8-bromo-6-chloro-3-methyl-imidazo[1,2-a]pyrazine (400 mg, 1.62 mmol, 1 eq) and K₂CO₃ (897.11 mg, 6.49 mmol, 4 eq) at 20°C. The reaction was stirred at 120°C for 3 h. LCMS showed starting material was consumed and desired product was detected. The reaction mixture was quenched by addition of water (10 mL) at 25°C, and then extracted with ethyl acetate (10 mL × 6). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 3/1) to give 6-chloro-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.15 g, 32% yield) as a white solid.

[00393] LCMS (ESI+): m/z 291 (M+H)⁺, RT: 0.573 min (Method G)

[00394] Synthesis of tert-butyl 3-[4-[3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00395] To a solution of tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (264.32 mg, 756.87 μmol, 2 eq) in THF (1 mL) and H₂O (0.1 mL) was added 6-chloro-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (110 mg, 378.43 μmol, 1 eq), K₃PO₄ (160.66 mg, 756.87 μmol, 2 eq) and [2-(2-aminophenyl)phenyl]-chloro-palladium dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (27.27 mg, 37.84 μmol, 0.1 eq) at 20°C. The reaction was stirred at 80°C for 12 h. TLC (petroleum ether:ethyl acetate = 1:2, R_f=0.15) showed starting material was consumed and desired product was detected. The reaction mixture was quenched by addition of water (20 mL) at 25°C, and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/2) to give tert-butyl 3-[4-[3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (0.175 g, 97% yield) as a white solid.

[00396] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00397] To a solution of tert-butyl 3-[4-[3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (110 mg, 230.38 μmol, 1 eq) in DCM (1.8 mL) was added TFA (0.4 mL) at 25°C. The reaction was stirred at 25°C for 0.5 h. LCMS showed starting material was consumed and desired product was detected. The reaction was concentrated to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (0.08 g, 92% yield) as a white solid.

[00398] LCMS (ESI+): m/z 378.1 (M+H)⁺, RT: 0.438 min (Method C)

[00399] Synthesis of 3-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

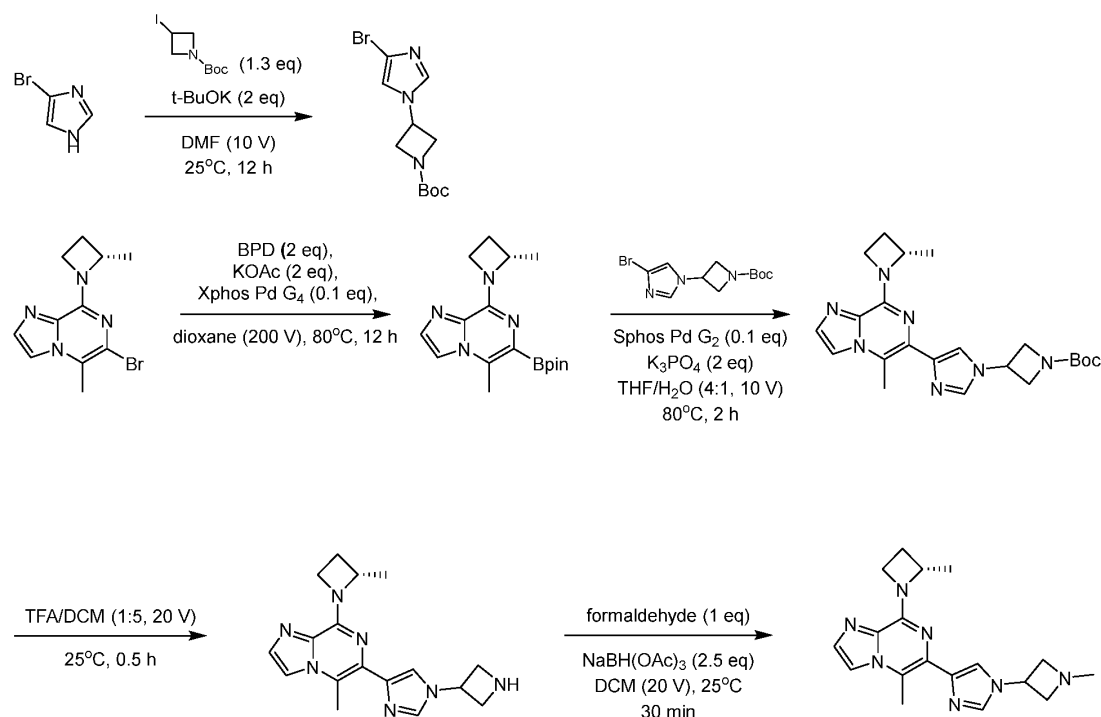
[00400] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-methyl-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (80 mg, 212.00 μmol, 1 eq) in DCM (0.8 mL) was added formaldehyde (17.21 mg, 212.00 μmol, 15.78 μL, 1

eq, purity 37%) and $\text{NaBH}(\text{OAc})_3$ (112.33 mg, 529.99 μmol , 2.5 eq) at 25°C. The reaction was stirred at 25°C for 1 h. LCMS showed starting material was consumed and desired product was detected. The reaction was concentrated and purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3 μm ; mobile phase: $[\text{H}_2\text{O}(0.1\%\text{TFA})\text{-ACN}]$; gradient: 1%-30% B over 8.0 min) to give 3-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (45 mg, 54% yield) as a white solid.

[00401] LCMS (ESI+): m/z 392.2 (M+H)⁺, RT: 2.582 min (Method F)

[00402] ^1H NMR (400 MHz, DMSO- d_6): δ = 8.19 (s, 1H), 8.17 (s, 1H), 8.07 (s, 1H), 7.38 (d, J = 0.7 Hz, 1H), 5.38-5.51 (m, 1H), 5.27 (dt, J = 9.1, 6.5 Hz, 1H), 4.34-4.73 (m, 6H), 3.02 (s, 3H), 2.66-2.79 (m, 1H), 2.51-2.56 (m, 1H), 2.48 (s, 3H)

EXAMPLE 13: Synthesis of Compound A22



[00403] Synthesis of tert-butyl 3-(4-bromoimidazol-1-yl)azetidine-1-carboxylate

[00404] To a solution of tert-butyl 3-iodoazetidine-1-carboxylate (12.52 g, 44.23 mmol, 1.3 eq) in DMF (50 mL) was added t-BuOK (7.63 g, 68.04 mmol, 2 eq) and 4-bromo-1H-imidazole (5 g, 34.02 mmol, 1 eq). The reaction was stirred at 25°C for 12 h. LCMS showed starting material was consumed and desired product was detected. The reaction mixture was quenched by addition of water (50 mL) at 25°C, and then extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD

C18 150*40mm*10um; mobile phase: [H₂O(10mM NH₄HCO₃)-ACN]; gradient:35%-65% B over 8.0 min) to give tert-butyl 3-(4-bromimidazol-1-yl)azetidine-1-carboxylate (3 g, 9.93 mmol, 29.18% yield) as a colorless oil.

[00405] LCMS (ESI+): m/z 302.1 (M+H)⁺, RT: 6.263 min (Method L)

[00406] ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.49 (d, J=1.43 Hz, 1 H) 7.16 (d, J=1.55 Hz, 1 H) 4.82 - 4.91 (m, 1 H) 4.40 - 4.51 (m, 2 H) 4.08 (dd, J=10.07, 4.95 Hz, 2 H) 1.48 (s, 10 H)

[00407] Synthesis of 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyrazine

[00408] To a solution of 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (1 g, 3556.8 μmol, 1 eq) in dioxane (200 mL) was added BPD (1.81 g, 7113.6 μmol, 2 eq), KOAc (698.1 mg, 7113.6 μmol, 2 eq) and dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane methanesulfonate [2[2(methylamino)phenyl]phenyl]palladium (306.1 mg, 355.7 μmol, 0.1 eq). The reaction was stirred at 80°C for 12 h. TLC (petroleum ether:ethyl acetate = 1:1, R_f=0.5) showed starting material was consumed and desired product was detected. The reaction mixture was quenched by addition of water (200 mL) at 25°C, and then extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyrazine (0.7 g, 60% yield) as a colorless oil.

[00409] Synthesis of tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-1-yl]azetidine-1-carboxylate

[00410] To a solution of tert-butyl 3-(4-bromimidazol-1-yl)azetidine-1-carboxylate (50 mg, 165.47 μmol, 1 eq) and 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyrazine (54.31 mg, 165.47 μmol, 1 eq) in THF (0.4 mL) and H₂O (0.1 mL) was added [2-(2-aminophenyl)phenyl]-chloro-palladium dicyclohexyl-[2-(2,6-dimethoxyphenyl)phenyl]phosphane (11.91 mg, 16.5 μmol, 0.1eq), K₃PO₄ (70.25 mg, 330.94 μmol, 2 eq). The reaction was stirred at 80°C for 2 h. LCMS showed starting material was consumed and desired product was detected. The reaction mixture was quenched by addition of water (10 mL) at 25°C, and then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-TLC to give tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-1-yl]azetidine-1-carboxylate (0.11 g, 20% yield) as a colorless oil.

[00411] LCMS (ESI+): m/z 424.0 (M+1)⁺, RT: 5.286 min (Method K)

[00412] Synthesis of 6-[1-(azetidin-3-yl)imidazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00413] A solution of tert-butyl 3-[4-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-1-yl]azetidine-1-carboxylate (90 mg, 212.51 μmol, 1 eq) in TFA (0.3 mL) and DCM (1.5 mL) was stirred at 25°C for 30 min. TLC (petroleum ether:ethyl acetate = 0:1) showed starting material was consumed and desired product was detected.

The reaction mixture was concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)imidazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (60 mg, 87% yield) as a colorless oil.

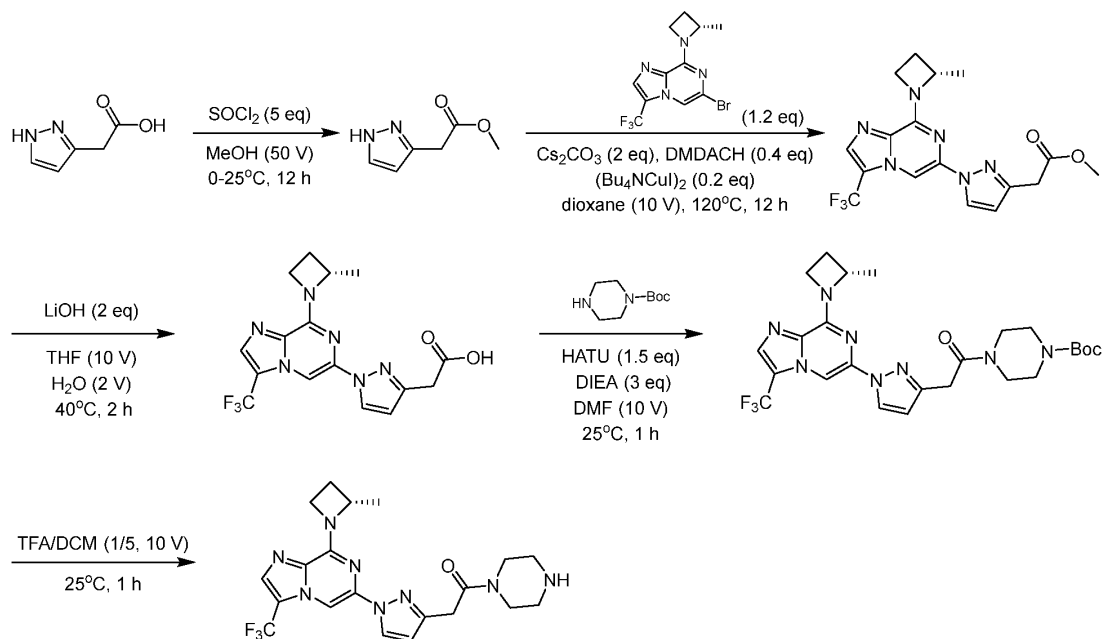
[00414] Synthesis of 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)imidazol-4-yl]imidazo[1,2-a]pyrazine

[00415] To a solution of 6-[1-(azetidin-3-yl)imidazol-4-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (45 mg, 139.15 μmol , 1 eq) in DCM (0.9 mL) was added $\text{NaBH}(\text{OAc})_3$ (73.73 mg, 347.87 μmol , 2.5 eq) and formaldehyde (11.29 mg, 139.15 μmol , 10.36 μL , 37% purity, 1 eq). The reaction was stirred at 25°C for 30 min. LCMS showed starting material was consumed and desired product was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3 μm ; mobile phase: $[\text{H}_2\text{O}(0.1\%\text{TFA})\text{-ACN}]$; gradient: 1%-30% B over 8.0 min) to give 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)imidazol-4-yl]imidazo[1,2-a]pyrazine (11.2 mg, 24% yield) as a colorless oil.

[00416] LCMS (ESI+): m/z 338.2 (M+H)⁺, RT: 2.307 min (Method F)

[00417] ^1H NMR (400 MHz, METHANOL- d_4) δ 7.89 (d, $J=1.31$ Hz, 1 H) 7.78 (d, $J=0.95$ Hz, 1 H) 7.65 (d, $J=1.31$ Hz, 1 H) 7.59 (d, $J=0.95$ Hz, 1 H) 4.98 (t, $J=6.79$ Hz, 1 H) 4.49 - 4.63 (m, 2 H) 4.28 (td, $J=8.97, 6.97$ Hz, 1 H) 3.84 - 3.91 (m, 2 H) 3.50 - 3.57 (m, 2 H) 2.71 (s, 3 H) 2.53 - 2.65 (m, 1 H) 2.47 (s, 3 H) 2.01 - 2.14 (m, 1 H) 1.60 (d, $J=6.20$ Hz, 3 H)

EXAMPLE 14: Synthesis of Compound A23



[00418] Synthesis of methyl 2-(1H-pyrazol-3-yl) acetate

[00419] To a solution of 2-(1H-pyrazol-3-yl)acetic acid (0.5 g, 3.96 mmol, 1 eq) in MeOH (25 mL) was added SOCl_2 (2.36 g, 19.82 mmol, 1.44 mL, 5 eq) at 0°C. The mixture was stirred at 25°C for 12 h. LCMS showed all starting

material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 4/1) to give methyl 2-(1H-pyrazol-3-yl) acetate (400 mg, 72% yield) as a white solid.

[00420] LCMS (ESI+): m/z 141.2 (M+H)⁺, RT: 0.155 min (Method D)

[00421] Synthesis of methyl 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetate

[00422] To a solution of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.4 g, 1.194 mmol, 1 eq) and methyl 2-(1H-pyrazol-3-yl)acetate (200.8 mg, 1.432 mmol, 1.2 eq) in dioxane (4 mL) was added Cs₂CO₃ (777.8 mg, 2.387 mmol, 2 eq), N1,N2-dimethylcyclohexane-1,2-diamine (68 mg, 477.4 μmol, 0.4 eq) and (Bu₄NCuI)₂ (267.2 mg, 238.8 μmol, 0.2 eq). The mixture was stirred at 120°C for 12 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/1) to give methyl 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetate (180 mg, 38% yield) as a white solid.

[00423] LCMS (ESI+): m/z 395.1 (M+1)⁺, RT: 0.625 min (Method D)

[00424] Synthesis of 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetic acid

[00425] To a solution of methyl 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetate (180 mg, 456.45 μmol, 1 eq) in THF (1.8 mL) and H₂O (0.36 mL) was added LiOH.H₂O (38.31 mg, 912.89 μmol, 2 eq). The mixture was stirred at 40°C for 2 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/1) to give 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetic acid (100 mg, 58% yield) as a white solid.

[00426] LCMS (ESI+): m/z 381.2 (M+H)⁺, RT: 0.510 min (Method D)

[00427] Synthesis of tert-butyl 4-[2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetyl]piperazine-1-carboxylate

[00428] To a solution of 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetic acid (100 mg, 262.93 μmol, 1 eq) and tert-butyl piperazine-1-carboxylate (53.87 mg, 289.23 μmol, 1.1 eq) in DMF (1 mL) was added DIEA (101.95 mg, 788.80 μmol, 137.39 μL, 3 eq) and HATU (149.96 mg, 394.40 μmol, 1.5 eq). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with

brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/1) to give tert-butyl 4-[2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetyl]piperazine-1-carboxylate (60 mg, 42% yield) as a white solid.

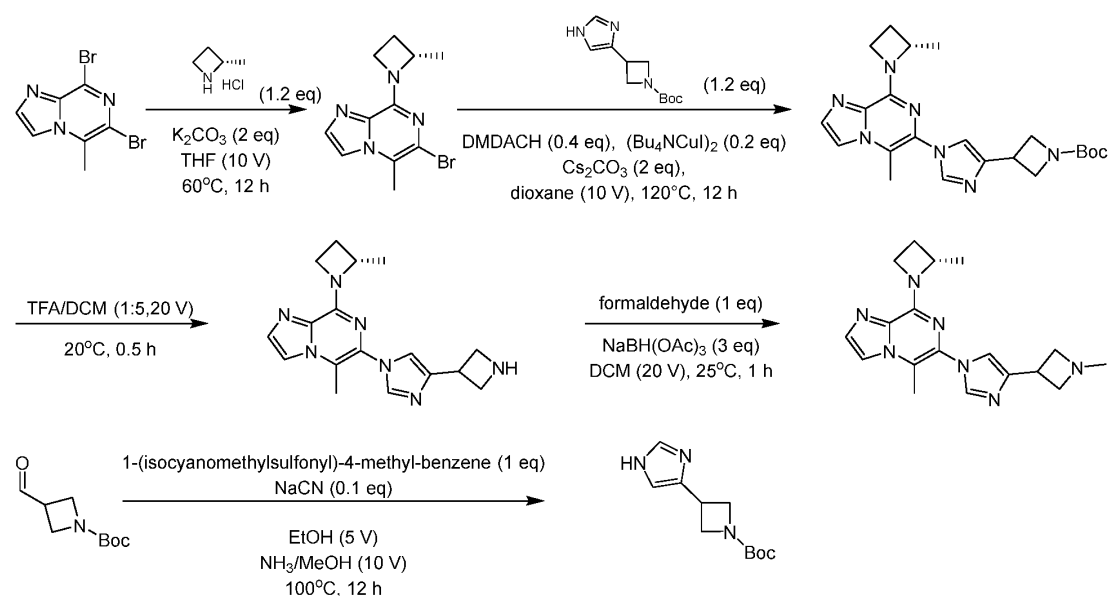
[00429] LCMS (ESI+): m/z 549.3 (M+H)⁺, RT: 0.624 min (Method D)

[00430] Synthesis of 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]-1-piperazin-1-yl-ethanone

[00431] A solution of tert-butyl 4-[2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]acetyl]piperazine-1-carboxylate (60 mg, 109.38 μmol, 1 eq) in DCM (0.5 mL) and TFA (0.1 mL) was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75×30 mm×3 μm; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 5%-30% B over 8.0 min) to give 2-[1-[8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-3-yl]-1-piperazin-1-yl-ethanone (30 mg, 61% yield) as a white solid.

[00432] LCMS (ESI+): m/z 449.2 (M+H)⁺, RT: 2.110 min (Method E)

EXAMPLE 15: Synthesis of Compound A24



[00433] Synthesis of 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00434] To a solution of 6,8-dibromo-5-methyl-imidazo[1,2-a]pyrazine (1.5 g, 5.16 mmol, 1 eq) and (2S)-2-methylazetidine (440.01 mg, 6.19 mmol, 1.2 eq) in THF (15 mL) was added K₂CO₃ (1.43 g, 10.32 mmol, 2 eq). The mixture was stirred at 60°C for 12 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (90 mL). The combined organic layers were washed with

brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/1) to give 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (1.2 g, 83% yield) as a white solid.

[00435] LCMS (ESI+): m/z 281.1 (M+H)⁺, RT: 0.532 min (Method C)

[00436] Synthesis of tert-butyl 3-(1H-imidazol-4-yl)azetidine-1-carboxylate

[00437] To a solution of tert-butyl 3-formylazetidine-1-carboxylate (2 g, 10.80 mmol, 1 eq) in EtOH (10 mL) and NH₃/MeOH (20 mL) was added 1-(isocyanomethylsulfonyl)-4-methylbenzene (2.11 g, 10.80 mmol, 1 eq) and NaCN (52.92 mg, 1.08 mmol, 0.1 eq). The mixture was stirred at 100°C for 12 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150×40mm×10um ;mobile phase: [H₂O (0.05% NH₃/H₂O+10mM NH₄HCO₃)-ACN]; gradient: 15%-45% B over 8.0 min) to give tert-butyl 3-(1H-imidazol-4-yl)azetidine-1-carboxylate (1 g, 41% yield) as a yellow solid.

[00438] LCMS (ESI+): m/z 168.0 (M-55)⁺, RT: 0.306 min (Method D)

[00439] Synthesis of tert-butyl 3-[1-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-4-yl]azetidine-1-carboxylate

[00440] To a solution of 6-bromo-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (100 mg, 355.68 μmol, 1 eq) and tert-butyl 3-(1H-imidazol-4-yl)azetidine-1-carboxylate (95.3 mg, 426.82 μmol, 1.2 eq) in dioxane (1 mL) was added Cs₂CO₃ (231.78 mg, 711.36 μmol, 2 eq), (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (20.24 mg, 142.28 μmol, 0.4 eq) and (Bu₄NCuI)₂ (79.64 mg, 71.14 μmol, 0.2 eq). The mixture was stirred at 120°C for 12 h under a N₂ atmosphere. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 1/1) to give tert-butyl 3-[1-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-4-yl]azetidine-1-carboxylate (90 mg, 60% yield) as a white solid.

[00441] LCMS (ESI+): m/z 424.4 (M+H)⁺, RT: 0.373 min (Method D)

[00442] Synthesis of 6-[4-(azetidin-3-yl)imidazol-1-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00443] A solution of tert-butyl 3-[1-[5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]imidazol-4-yl]azetidine-1-carboxylate (90 mg, 212.5 μmol, 1 eq) in a mixture of DCM (1.5 mL) and TFA (0.3 mL) was stirred at 20°C for 0.5 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction was concentrated under reduced pressure to give the product (60 mg, 87% yield) as a white solid.

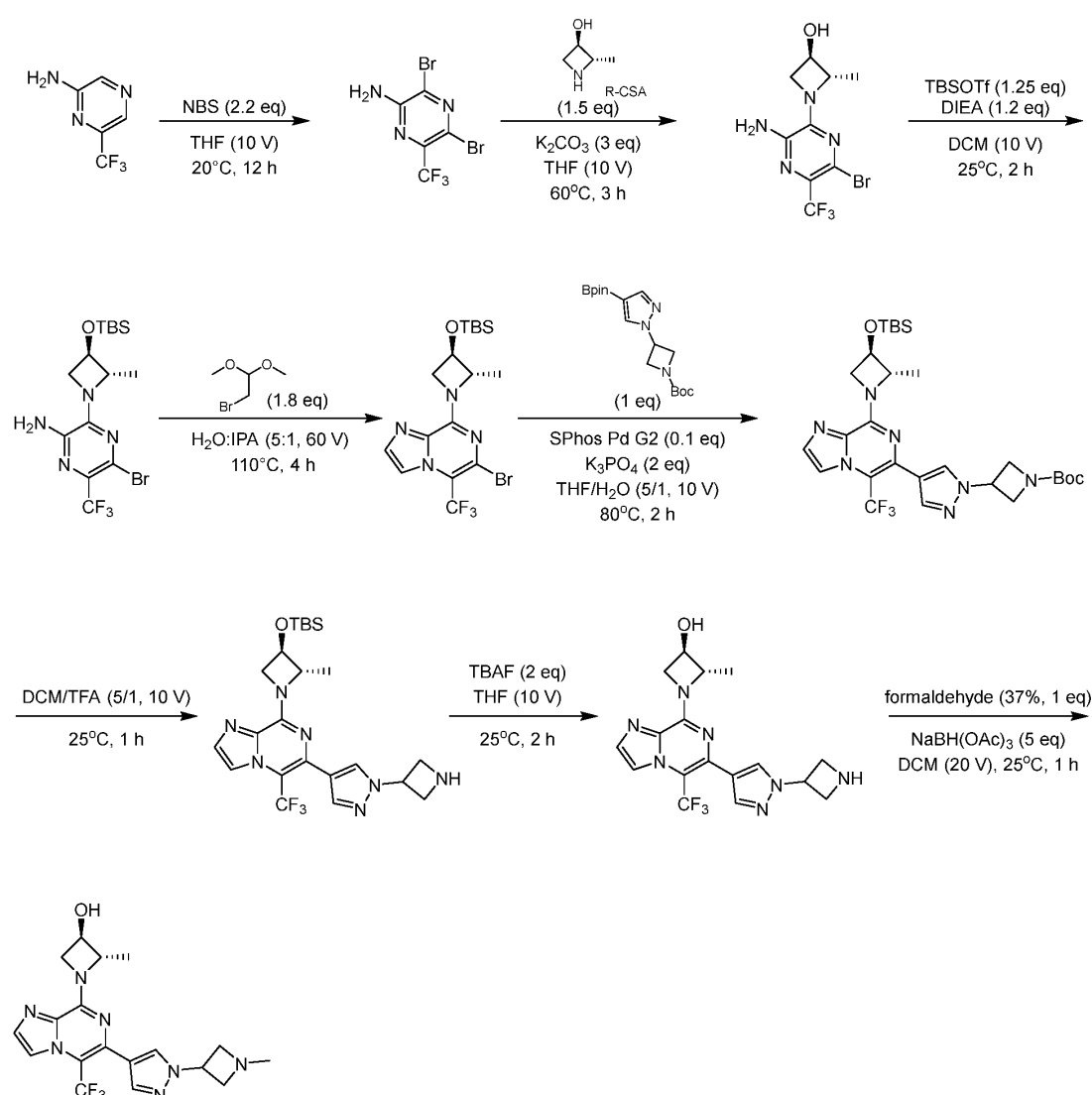
[00444] LCMS (ESI+): m/z 324.1 (M+H)⁺, RT: 0.287 min (Method D)

[00445] Synthesis of 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[4-(1-methylazetidin-3-yl)imidazol-1-yl]imidazo[1,2-a]pyrazine

[00446] To a solution of 6-[4-(azetidin-3-yl)imidazol-1-yl]-5-methyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (60 mg, 185.53 μ mol, 1 eq) in DCM (1.2 mL) was added formaldehyde (5.63 mg, 187.41 μ mol, 1 eq) and $\text{NaBH}(\text{OAc})_3$ (119.16 mg, 563.63 μ mol, 3 eq). The mixture was stirred at 25°C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass. The reaction mixture was extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 $\times$ 30mm $\times$ 3 μ m; mobile phase: $[\text{H}_2\text{O}(0.1\%\text{TFA})\text{-ACN}]$; gradient: 5%-35% B over 8.0 min) to give 5-methyl-8-[(2S)-2-methylazetidin-1-yl]-6-[4-(1-methylazetidin-3-yl)imidazol-1-yl]imidazo[1,2-a]pyrazine (40 mg, 64% yield) as a white solid.

[00447] LCMS (ESI+): m/z 338.1 (M+H)⁺, RT: 1.587 min (Method E)

EXAMPLE 16: Synthesis of Compound A25



[00448] Synthesis of 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine

[00449] To a solution of 6-(trifluoromethyl) pyrazin-2-amine (3.5 g, 21.46 mmol, 1 eq) in THF (35 mL) was added NBS (8.4 g, 47.21 mmol, 2.2 eq). The mixture was stirred at 20°C for 12 h. TLC and LCMS showed all starting material was consumed and new product was formed. The reaction mixture was diluted with H₂O (30 mL) and extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with brine (40 mL × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 10:1 to 3:1, (TLC: petroleum ether:ethyl acetate = 1:1, R_f=0.4) to give 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine (1.5 g, 22% yield) as a yellow solid.

[00450] ¹H NMR (400 MHz, DMSO-d₆) δ 7.34-7.76 (m, 2H)

[00451] Synthesis of (2S,3R)-1-[3-amino-6-bromo-5-(trifluoromethyl)pyrazin-2-yl]-2-methyl-azetidin-3-ol

[00452] To a solution of 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine (1.35 g, 4.20 mmol, 1 eq) in THF (13.5 mL) was added K₂CO₃ (1.74 g, 12.63 mmol, 3 eq) and (2S,3R)-2-methylazetidin-3-ol (579.48 mg, 6.30 mmol, 1.5 eq, R-CSA salt). The mixture was stirred at 60°C for 3 h. TLC and LCMS showed all starting material was consumed and a new product was formed. The reaction mixture was diluted with H₂O (20 mL) and extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine (20 mL × 4), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:1) to give (2S,3R)-1-[3-amino-6-bromo-5-(trifluoromethyl)pyrazin-2-yl]-2-methyl-azetidin-3-ol (750 mg, 55% yield) as a white solid.

[00453] LCMS (ESI+): m/z 325.0 (M-H)⁺, RT: 0.488 min (Method M)

[00454] Synthesis of 5-bromo-3-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-6-(trifluoromethyl)pyrazin-2-amine

[00455] To a solution of (2S,3R)-1-[3-amino-6-bromo-5-(trifluoromethyl)pyrazin-2-yl]-2-methyl-azetidin-3-ol (650 mg, 1.98 mmol, 1 eq) in DCM (6.5 mL) was added TBSOTf (656.63 mg, 2.48 mmol, 570.44 μL, 1.25 eq) and DIEA (355.5 mg, 2.38 mmol, 415.2 μL, 1.2 eq). The mixture was stirred at 25°C for 2 h. LCMS showed all starting material was consumed. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM (30 mL × 2). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:1) to give 5-bromo-3-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-6-(trifluoromethyl) pyrazin-2-amine (550 mg, 63% yield) as a yellow oil.

[00456] LCMS (ESI+): m/z 443.0 (M+H)⁺, RT: 0.745 min (Method D)

[00457] Synthesis of [(2S,3R)-1-[6-bromo-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane

[00458] To a solution of 5-bromo-3-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-6-(trifluoromethyl)pyrazin-2-amine (500 mg, 1.13 mmol, 1 eq) in H₂O (25 mL) and IPA (5 mL) was added 2-bromo-1,1-dimethoxy-ethane (664.86 mg, 2.03 mmol, 239.32 μL, 1.8 eq). The mixture was stirred at 110°C for 4 h. TLC

(petroleum ether:ethyl acetate = 3:1, Rf=0.3) showed all starting material was consumed and one new product formed. The reaction mixture was extracted with DCM (30 mL × 2). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:1) to give [(2S,3R)-1-[6-bromo-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane (170 mg, 32 % yield) as a yellow oil.

[00459] LCMS (ESI+): m/z 465(M+1)+, RT: 2.829 (Method A)

[00460] Synthesis of tert-butyl 3-[4-[8-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00461] To a solution of [(2S,3R)-1-[6-bromo-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane (190 mg, 408.27 μmol, 1 eq) in THF (1.67 mL) and H₂O (0.33 mL) was added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (142.57 mg, 408.27 μmol, 1 eq), [2-(2-aminophenyl)phenyl]-chloro-palladium dicyclohexyl-[2-(2,6-dimethoxyphenyl) phenyl] phosphane (29.42 mg, 40.83 μmol, 0.1 eq) and K₃PO₄ (173.31 mg, 816.52 μmol, 2 eq). The mixture was stirred at 80°C for 2 h. LCMS showed all starting material was consumed completely and desired mass was detected. The reaction mixture was diluted with H₂O (5 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:1) to give tert-butyl 3-[4-[8-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (150 mg, 60% yield) as a yellow solid.

[00462] LCMS (ESI+): m/z 608.3 (M+1)+, RT: 0.77 min (Method D)

[00463] Synthesis of [(2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane

[00464] A solution of tert-butyl 3-[4-[8-[(2S,3R)-3-[tert-butyl(dimethyl)silyl]oxy-2-methyl-azetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (150 mg, 246.82 μmol, 1 eq) in DCM (1.25 mL) and TFA (0.25 mL) was stirred at 25°C for 1 h. TLC (petroleum ether:ethyl acetate = 1:1, Rf = 0.3) showed all starting material was completely consumed and one new product generated. The reaction mixture was filtered and concentrated under reduced pressure to give [(2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane (110 mg, 90% yield) as a yellow oil, which was used for the next step directly without purification.

[00465] LCMS (ESI+): m/z 508.2 (M+1)+, RT: 0.52 min (Method D)

[00466] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00467] To a solution of [(2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl]oxy-tert-butyl-dimethyl-silane (110 mg, 197 μmol, 1 eq) in THF (1.1 mL) was added

tetrabutylammonium fluoride trihydrate (1 M, 394 μ L, 2 eq). The mixture was stirred at 25 °C for 2 h. LCMS showed starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (60 mg, 70% yield) as a yellow oil, which was used for the next step directly without purification.

[00468] LCMS (ESI+): m/z 394.1 (M+H)⁺, RT: 0.316 min (Method D)

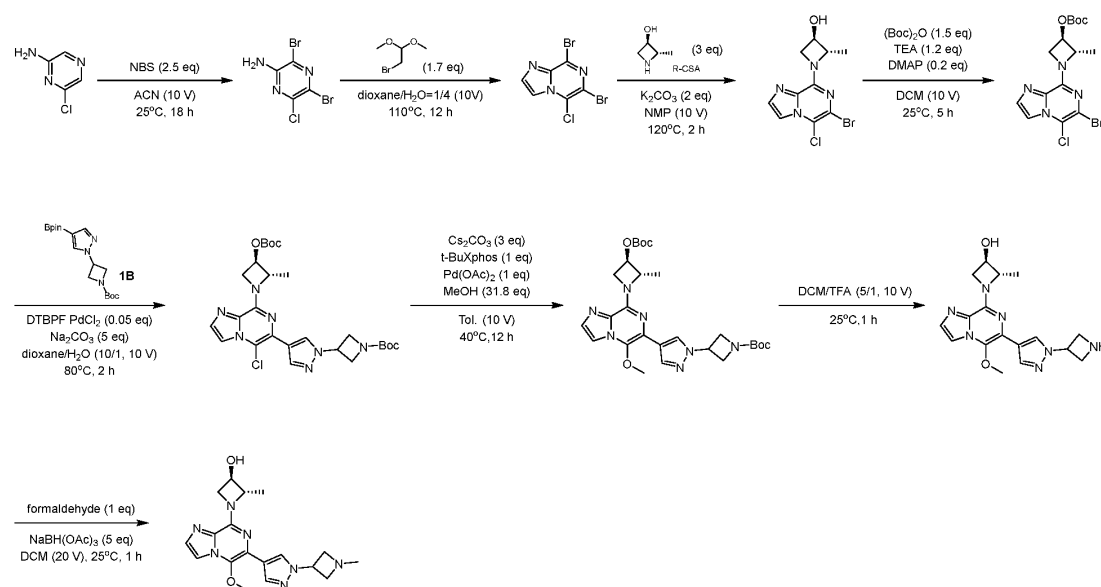
[00469] Synthesis of (2S,3R)-2-methyl-1-[6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol

[00470] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (60 mg, 152.53 μ mol, 1 eq) in DCM (1.2 mL) was added formaldehyde (12.35 mg, 152.53 μ mol, 11.35 μ L, 37%, 1 eq) and NaBH(OAc)₃ (161.62 mg, 762.65 μ mol, 5 eq). The mixture was stirred at 25 °C for 1 h. LCMS showed all starting material was consumed and a new peak with desired mass was detected. The reaction mixture was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 5%-40% B over 8.0 min) to give (2S,3R)-2-methyl-1-[6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol (25 mg, 40% yield) as a yellow solid.

[00471] LCMS (ESI+): m/z 408.2 (M+H)⁺, RT: 2.418 min (Method F)

[00472] ¹H NMR (400 MHz, DMSO-d₆) δ 1.63 (d, J=6.48 Hz, 3H), 3.02-3.22 (m, 3H), 4.23 (br s, 2H), 4.46-4.64 (m, 3H), 4.67-4.77 (m, 1H), 4.87-4.96 (m, 2H), 5.37-5.52 (m, 1H), 7.64-7.67 (m, 1H), 7.88-7.91 (m, 2H), 7.99 (s, 1H)

EXAMPLE 17: Synthesis of Compound A26



[00473] Synthesis of 3,5-dibromo-6-chloro-pyrazin-2-amine

[00474] To a solution of 6-chloropyrazin-2-amine (1 g, 7.72 mmol, 1 eq) in acetonitrile (10 mL) was added NBS (3.43 g, 19.30 mmol, 2.5 eq). The mixture was stirred at 25°C for 18 hours. LCMS showed the starting material was consumed and one main peak with desired mass. The reaction mixture was quenched by addition of water (13 mL), and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (17 mL × 7), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0–5% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) (TLC: petroleum ether:ethyl acetate = 3:1, R_f=0.4) to give 3,5-dibromo-6-chloro-pyrazin-2-amine (2 g, 90% yield) as a yellow solid.

[00475] LCMS (ESI+): m/z 285.9 (M+1)⁺, RT: 0.546 min (Method C)

[00476] ¹H NMR (400 MHz, CDCl₃, 298 K) δ (ppm) = 5.17 (br s, 2H)

[00477] Synthesis of 6,8-dibromo-5-chloro-imidazo[1,2-a]pyrazine

[00478] To a solution of 2-bromo-1,1-dimethoxy-ethane (2.00 g, 11.83 mmol, 1.39 mL, 1.7 eq) in dioxane (4 mL) and H₂O (16 mL) was added 3,5-dibromo-6-chloro-pyrazin-2-amine (2 g, 6.96 mmol, 1 eq). The mixture was stirred at 110°C for 12 hours. LCMS showed the starting material was consumed and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give 6,8-dibromo-5-chloro-imidazo[1,2-a]pyrazine (2 g, 92% yield) as a brown solid.

[00479] LCMS (ESI+): m/z 309.9 (M+1)⁺, RT: 0.490 min (Method C)

[00480] Synthesis of (2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol

[00481] To a solution of 6,8-dibromo-5-chloro-imidazo[1,2-a]pyrazine (500 mg, 1.61 mmol, 1 eq) and (2S,3R)-2-methylazetidin-3-ol (419.71 mg, 4.82 mmol, 3 eq) in NMP (5 mL) was added K₂CO₃ (443.88 mg, 3.21 mmol, 2 eq). The mixture was stirred at 120°C for 2 hours. Three additional vials in 500 mg scale were set up as described above. LCMS showed the starting material was consumed and one main peak with desired mass. The reaction mixture was quenched by addition of water (35 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 5–15% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) (TLC: petroleum ether:ethyl acetate = 1:3, R_f=0.5) to give (2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (1.4 g, 69% yield) as a yellow oil.

[00482] LCMS (ESI+): m/z 316.9 (M+1)⁺, RT: 0.443 min (Method D)

[00483] Synthesis of [(2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate

[00484] To a solution of (2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (1.2 g, 3.78 mmol, 1 eq) in dichloromethane (12 mL) was added (Boc)₂O (1.24 g, 5.67 mmol, 1.30 mL, 1.5 eq), trimethylamine

(458.84 mg, 4.53 mmol, 631.14 μ L, 1.2 eq) and DMAP (92.33 mg, 755.74 μ mol, 0.2 eq). The mixture was stirred at 25°C for 5 hours. LCMS showed the starting material was consumed and one main peak with desired mass. The reaction mixture was quenched by addition of water (25 mL), and extracted with dichloromethane (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL $\times$ 7), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 20–30% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) (TLC: petroleum ether:ethyl acetate = 1:2, R_f=0.4) to give [(2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate (1 g, 63% yield) as a colourless oil.

[00485] LCMS (ESI+): m/z 417.0 (M+1)⁺, RT: 0.656 min (Method D)

[00486] Synthesis of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-chloro-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00487] A mixture of tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (836.11 mg, 2.39 mmol, 1 eq), [(2S,3R)-1-(6-bromo-5-chloro-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate (1 g, 2.39 mmol, 1 eq), Na₂CO₃ (1.27 g, 11.97 mmol, 5 eq) and di-tert-butyl(cyclopentyl)phosphane dichloropalladium iron (78.02 mg, 119.71 μ mol, 0.05 eq) in H₂O (1 mL) and dioxane (10 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 80°C for 2 hours under a N₂ atmosphere. LCMS showed the starting material was consumed completely and desired mass was detected. The reaction mixture was quenched by addition of water (30 mL), and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (35 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 30–40% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) (TLC: petroleum ether:ethyl acetate = 2:1, R_f=0.5) to give tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-chloro-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (850 mg, 63% yield) as a white solid.

[00488] LCMS (ESI+): m/z 560.2 (M+1)⁺, RT: 0.653 min (Method D)

[00489] Synthesis of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methoxy-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00490] A mixture of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-chloro-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (50 mg, 89.28 μ mol, 1 eq), methanol (90.96 mg, 2.84 mmol, 114.88 μ L, 31.8 eq), Cs₂CO₃ (87.27 mg, 267.84 μ mol, 3 eq), di-tert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (37.91 mg, 89.28 μ mol, 1 eq) and diacetoxypalladium (20.04 mg, 89.28 μ mol, 1 eq) in toluene (1 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 40°C for 12 hours under a N₂ atmosphere. LCMS showed the starting material was consumed and desired mass was detected. Eighteen additional vials in 50 mg scale were set up as described above. The mixture was filtered and the filter cake was washed with ethyl acetate (20 mL). The combined organic layer was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 40–60% Ethyl acetate/Petroleum ether

gradient @ 80 mL/min) (TLC: petroleum ether:ethyl acetate = 2:1, Rf=0.3) to give tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methoxy-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (100 mg, 11% yield) as a yellow solid.

[00491] LCMS (ESI+): m/z 556.3 (M+1)+, RT: 0.560 min (Method D)

[00492] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methoxy-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00493] A solution of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methoxy-imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (80 mg, 143.98 μ mol, 1 eq) in dichloromethane (1 mL) and trifluoroacetic acid (0.2 mL) was stirred at 25°C for 1 hour. LCMS showed the starting material was consumed and one main peak with desired mass was detected. The reaction mixture was adjusted to pH=7-8 with aqueous NaHCO₃, and extracted with ethyl acetate (1 mL $\times$ 3). The combined organic layers were washed with brine (2 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methoxy-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (36 mg, 70% yield) as a white solid.

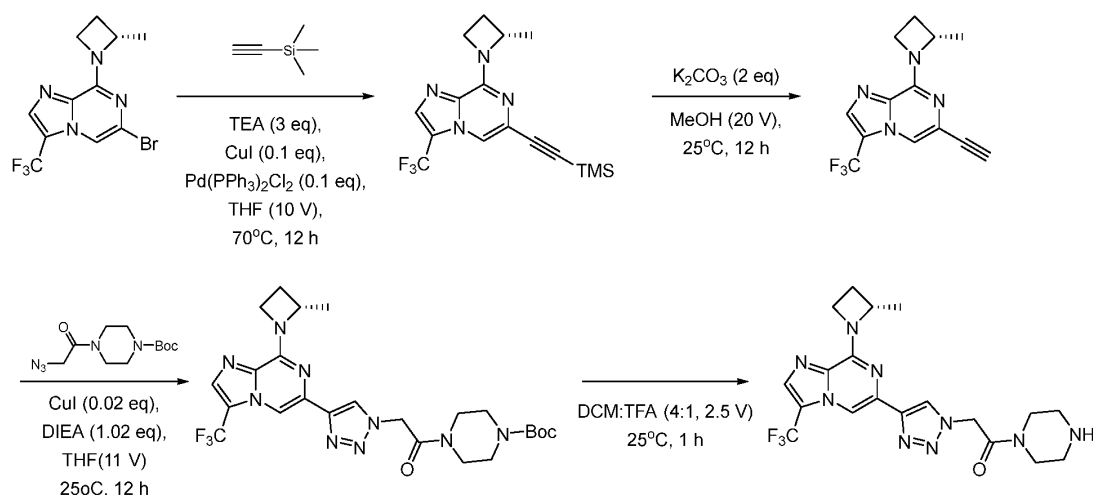
[00494] LCMS (ESI+): m/z 356.1 (M+1)+, RT: 0.097 min (Method D)

[00495] Synthesis of (2S,3R)-1-[5-methoxy-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00496] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methoxy-imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (36 mg, 101.30 μ mol, 1 eq) in dichloromethane (1 mL) was added formaldehyde (3.04 mg, 101.30 μ mol, 2.79 μ L, 1 eq) and NaBH(OAc)₃ (107.34 mg, 506.48 μ mol, 5 eq). The mixture was stirred at 25°C for 1 hour. LCMS showed the starting material was consumed and desired mass was detected. The residue was filtered and purified by prep-HPLC (TFA condition: column: Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient: 1%-30% B over 8.0 min) to give (2S,3R)-1-[5-methoxy-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (10.3 mg, 28% yield) as a yellow solid.

[00497] LCMS (ESI+): m/z 370.2 (M+1)+, RT: 1.597 min (Method I)

EXAMPLE 18: Synthesis of Compound A27



[00498] Synthesis of (S)-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine

[00499] To a solution of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.45 g, 1.34 mmol, 1 eq) in THF (4.5 mL) was added TEA (407.63 mg, 4.03 mmol, 560.70 μL , 3 eq), ethynyl(trimethyl)silane (1.32 g, 13.43 mmol, 1.86 mL, 10 eq), CuI (25.57 mg, 134.28 μmol , 0.1 eq) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (94.25 mg, 134.28 μmol , 0.1 eq). The mixture was stirred at 70°C for 12 h. LCMS showed desired compound was detected. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL $\times$ 2). The combined organic layers were washed with aqueous sodium chloride (5 mL $\times$ 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2 , petroleum ether:ethyl acetate = 5:1) to give (S)-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine (317 mg, 67% yield) as a colourless oil.

[00500] LCMS (ESI+): m/z 353.2 (M+H)⁺, RT: 0.751 min (Method C)

[00501] Synthesis of (S)-6-ethynyl-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazine

[00502] To a solution of (S)-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)-6-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyrazine (269 mg, 763.27 μmol , 1 eq) in methanol (5 mL) was added K_2CO_3 (210.98 mg, 1.53 mmol, 2 eq). The mixture was stirred at 25°C for 12 h. LCMS showed desired compound was detected. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL $\times$ 2). The combined organic layers were washed with aqueous sodium chloride (5 mL $\times$ 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give (S)-6-ethynyl-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (200 mg, 94% yield), which was used in the next step without further purification.

[00503] LCMS (ESI+): m/z 281.0 (M+H)⁺, RT: 0.553 min (Method D)

[00504] Synthesis of tert-butyl (S)-4-(2-(4-(8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)-1H-1,2,3-triazol-1-yl)acetyl)piperazine-1-carboxylate

[00505] To a solution of (S)-6-ethynyl-8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazine (172.97 mg, 642.29 μmol , 1 eq) in THF (2 mL) was added tert-butyl 4-(2-azidoacetyl)piperazine-1-carboxylate (0.18 g, 642.29 μmol ,

1 eq), CuI (2.45 mg, 12.85 μ mol, 0.02 eq) and DIEA (84.67 mg, 655.13 μ mol, 114.11 μ L, 1.02 eq). The mixture was stirred at 25°C for 12 h. LCMS showed desired compound was detected. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 mL $\times$ 2). The combined organic layers were washed with aqueous sodium chloride (3 mL $\times$ 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (SiO₂, petroleum ether:ethyl acetate = 1:1) to give tert-butyl (S)-4-(2-(4-(8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)-1H-1,2,3-triazol-1-yl)acetyl)piperazine-1-carboxylate (0.2 g, 57% yield) as a colourless oil.

[00506] LCMS (ESI+): m/z 550.2 (M+H)⁺, RT: 0.555 min (Method D)

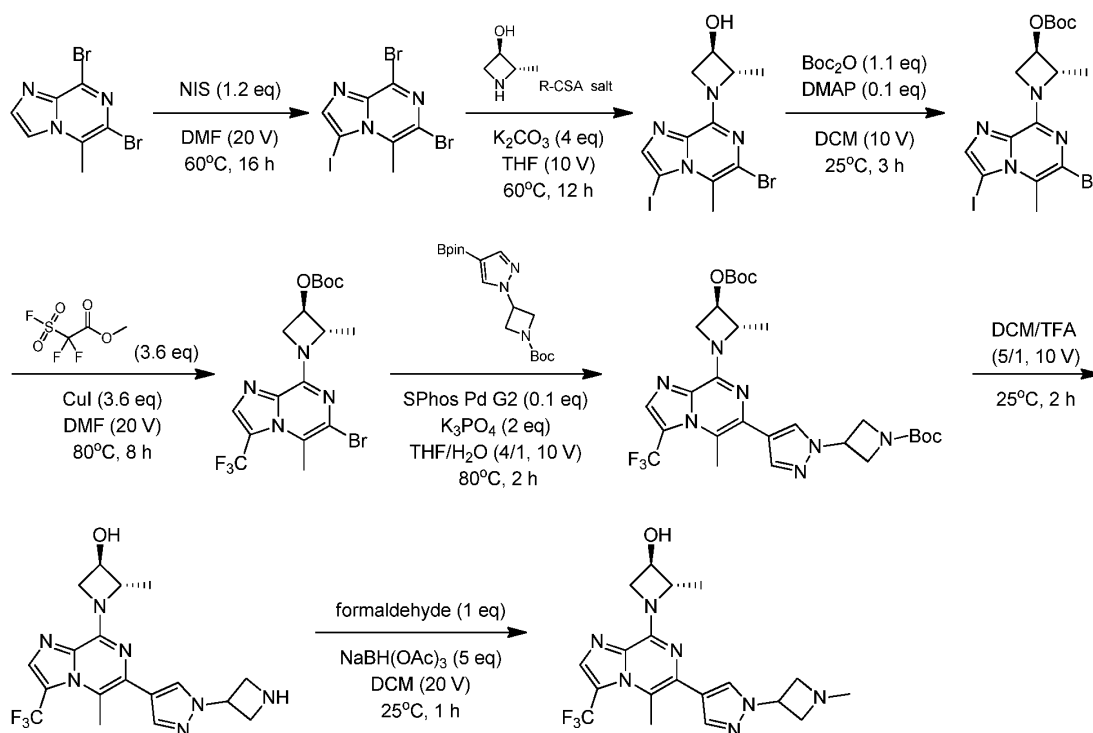
[00507] Synthesis of (S)-2-(4-(8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)-1H-1,2,3-triazol-1-yl)-1-(piperazin-1-yl)ethan-1-one

[00508] To a solution of tert-butyl (S)-4-(2-(4-(8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)-1H-1,2,3-triazol-1-yl)acetyl)piperazine-1-carboxylate (0.1 g, 181.97 μ mol, 1 eq) in DCM (0.2 mL) was added TFA (0.05 mL). The mixture was stirred at 25°C for 1 h. LCMS showed desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition) to give (S)-2-(4-(8-(2-methylazetidin-1-yl)-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl)-1H-1,2,3-triazol-1-yl)-1-(piperazin-1-yl)ethan-1-one (0.05 g, 61% yield) as a white solid.

[00509] LCMS (ESI+): m/z 450.2 (M+H)⁺, RT: 1.412 min (Method A)

[00510] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.27 - 8.32 (m, 1 H) 8.22 - 8.27 (m, 1 H) 7.91 - 7.97 (m, 1 H) 5.60 (s, 2 H) 4.89 - 4.99 (m, 1 H) 4.41 - 4.67 (m, 2 H) 3.82 - 3.95 (m, 4 H) 3.38 (br s, 2 H) 3.24 - 3.30 (m, 2 H) 2.54 - 2.76 (m, 1 H) 2.05 - 2.21 (m, 1 H) 1.68 (d, J=6.20 Hz, 3 H)

EXAMPLE 19: Synthesis of Compound A28



[00511] Synthesis of 6,8-dibromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazine

[00512] To a solution of 6,8-dibromo-5-methyl-imidazo[1,2-a]pyrazine (4 g, 13.76 mmol, 1 eq) in DMF (80 mL) was added NIS (3.71 g, 16.48 mmol, 1.2 eq). The mixture was stirred at 60°C for 16 hrs. LCMS showed starting material was consumed and one main peak with desired product was detected. The reaction mixture was poured into water, the solid was collected by filtration and dried under reduced pressure to give 6,8-dibromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazine (3.9 g, yield 68.05%) as a white solid, which was used for the next step without purification.

[00513] LCMS (ESI+): m/z 415.8, 417.8 (M+H, M+3)+, RT: 0.441 min (Method N)

[00514] ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 (s, 1 H) 3.17 (s, 3 H)

[00515] Synthesis of (2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol

[00516] To a solution of 6,8-dibromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazine (1 g, 2.40 mmol, 1 eq) in THF (10 mL) was added K₂CO₃ (1.32 g, 9.60 mmol, 4 eq) and (2S,3R)-2-methylazetidin-3-ol (766.28 mg, 2.40 mmol, 1 eq, R-CSA salt). The mixture was stirred at 60°C for 12 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified on silica gel, eluting with petroleum ether:ethyl acetate = 1:0 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.5) to give (2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (810 mg, yield 79.81%) as an orange solid.

[00517] LCMS (ESI+): m/z 422.9, 424.9 (M+H, M+3)+, RT: 0.379 min (Method N)

[00518] ¹H NMR (400 MHz, DMSO-d₆) δ 7.60 (s, 1H), 5.68 (d, 1H, J = 6.5 Hz), 4.5-4.6 (m, 1H), 4.31 (br d, 1H, J = 5.0 Hz), 4.0-4.2 (m, 1H), 3.90 (br dd, 1H, J = 4.6, 9.9 Hz), 3.01 (s, 3H), 1.48 (d, 3H, J = 6.4 Hz)

[00519] Synthesis of [(2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate

[00520] To a solution of (2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-ol (650 mg, 1.53 mmol, 1 eq) in DCM (6.5 mL) was added Boc₂O (369.42 mg, 1.69 mmol, 388.87 μL, 1.1 eq) and DMAP (18.80 mg, 153.87 μmol, 0.1 eq). The mixture was stirred at 25°C for 3 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluted with petroleum ether:ethyl acetate = 1:0 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.7) to give [(2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate (600 mg, yield 74.64%) as a pale-yellow oil.

[00521] LCMS (ESI+): m/z 522.9, 524.9 (M+H, M+3)⁺, RT: 0.518 min (Method N)

[00522] ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (s, 1H), 4.8-4.8 (m, 1H), 4.6-4.7 (m, 1H), 4.54 (br s, 1H), 4.1-4.1 (m, 1H), 3.02 (s, 3H), 1.57 (d, 3H, J = 6.4 Hz), 1.42 (s, 9H)

[00523] Synthesis of [(2S,3R)-1-[6-bromo-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl] tert-butyl carbonate

[00524] To a solution of [(2S,3R)-1-(6-bromo-3-iodo-5-methyl-imidazo[1,2-a]pyrazin-8-yl)-2-methyl-azetidin-3-yl] tert-butyl carbonate (600 mg, 1.15 mmol, 1 eq) in DMF (12 mL) was added CuI (786.32 mg, 4.13 mmol, 3.6 eq) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (793.19 mg, 4.13 mmol, 525.29 μL, 3.6 eq). The mixture was stirred at 80°C for 8 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to 20°C, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 1:0 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.5) to give [(2S,3R)-1-[6-bromo-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl] tert-butyl carbonate (450 mg, yield 71.68%) as a pale-yellow oil.

[00525] LCMS (ESI+): m/z 465.0, 467.0 (M+H, M+3)⁺, RT: 0.534 min (Method N)

[00526] ¹H NMR (400 MHz, DMSO-d₆) δ 8.21 (s, 1H), 4.8-4.9 (m, 1H), 4.7-4.8 (m, 1H), 4.60 (br d, 1H, J = 1.6 Hz), 4.20 (br d, 1H, J = 8.3 Hz), 2.63 (br s, 3H), 1.60 (br d, 3H, J = 6.4 Hz), 1.43 (s, 9H)

[00527] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -52.9-47.0 (m, 3F)

[00528] Synthesis of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00529] To a solution of [(2S,3R)-1-[6-bromo-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-yl] tert-butyl carbonate (450 mg, 967.18 μ mol, 1 eq) in the mixture of H₂O (0.9 mL) and THF (3.6 mL) was added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (405.34 mg, 1.16 mmol, 1.2 eq), [2-(2-aminophenyl)phenyl]-chloro-palladium dicyclohexyl-[2-(2,6-dimethoxyphenyl) phenyl] phosphane (69.71 mg, 96.73 μ mol, 0.1 eq) and K₃PO₄ (410.60 mg, 1.93 mmol, 2 eq) under nitrogen. The mixture was stirred at 80°C for 2 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to 20°C, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 1:0 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.4) to give tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a] pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (300 mg, yield 51.05%) as a brown oil.

[00530] LCMS (ESI+): m/z 608.2 (M+H)⁺, RT: 0.612 min (Method N)

[00531] ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (d, 2H, J = 5.8 Hz), 7.93 (s, 1H), 5.2-5.3 (m, 1H), 4.85 (td, 1H, J = 4.1, 6.1 Hz), 4.75 (br dd, 1H, J = 6.5, 10.1 Hz), 4.5-4.6 (m, 1H), 4.3-4.3 (m, 2H), 4.2-4.2 (m, 2H), 4.12 (br d, 1H, J = 6.3 Hz), 2.65 (br s, 3H), 1.63 (d, 3H, J = 6.4 Hz), 1.4-1.4 (m, 18H)

[00532] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -49.68 (s, 3F)

[00533] Synthesis of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol

[00534] To a solution of tert-butyl 3-[4-[8-[(2S,3R)-3-tert-butoxycarbonyloxy-2-methyl-azetidin-1-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (300 mg, 493.73 μ mol, 1 eq) in DCM (2.5 mL) was added TFA (0.5 mL). The mixture was stirred at 25°C for 2 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (200 mg, yield 99.04%) as a brown oil, which was used for the next step without purification.

[00535] LCMS (ESI+): m/z 408.1 (M+H)⁺, RT: 0.306 min (Method N)

[00536] ¹H NMR (400 MHz, DMSO-d₆) δ 8.2-8.3 (m, 2H), 8.0-8.0 (m, 1H), 5.51 (br t, 1H, J = 7.4 Hz), 4.66 (br t, 1H, J = 7.5 Hz), 4.3-4.5 (m, 7H), 4.16 (br d, 1H, J = 4.8 Hz), 3.98 (br dd, 1H, J = 4.1, 9.4 Hz), 2.6-2.7 (m, 3H), 1.5-1.6 (m, 3H)

[00537] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -49.78 (br s, 3F)

[00538] Synthesis of (2S,3R)-2-methyl-1-[5-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol

[00539] To a solution of (2S,3R)-1-[6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]-2-methyl-azetidin-3-ol (200 mg, 490.93 μ mol, 1 eq) in DCM (0.3 mL) was added formaldehyde (39.84 mg, 490.93 μ mol, 36.55 μ L, 37% purity, 1 eq) and NaBH(OAc)₃ (520.24 mg, 2.45 mmol, 5 eq). The mixture was stirred at 25°C for 1

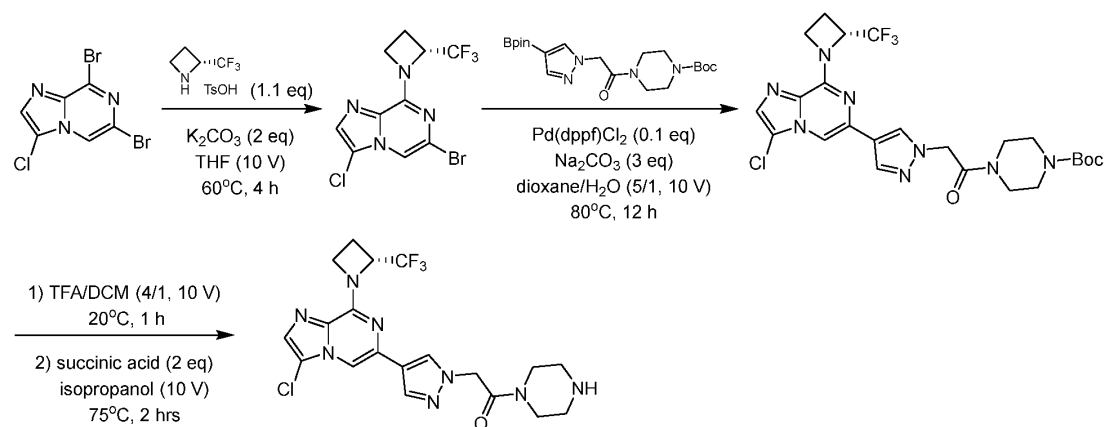
hr. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 150 * 25 mm * 5 um; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 26%-56% B over 10 min to give (2S,3R)-2-methyl-1-[5-methyl-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-3-(trifluoromethyl)imidazo[1,2-a]pyrazin-8-yl]azetidin-3-ol (110 mg, yield 50.51%) as a brown solid.

[00540] LCMS (ESI+): m/z 422.3 (M+H)⁺, RT: 1.870 min (Method P)

[00541] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.06 (s, 1H), 8.01 (s, 1H), 7.88 (s, 1H), 5.09 (quin, 1H, J = 7.1 Hz), 4.77 (dd, 1H, J = 6.9, 9.1 Hz), 4.49 (quin, 1H, J = 5.7 Hz), 4.2-4.3 (m, 1H), 4.06 (dd, 1H, J = 4.9, 9.8 Hz), 3.9-3.9 (m, 2H), 3.6-3.7 (m, 2H), 2.70 (d, 3H, J = 1.3 Hz), 2.50 (s, 3H), 1.61 (d, 3H, J = 6.3 Hz)

[00542] ¹⁹F NMR (400 MHz, METHANOL-d₄) δ -52.33 (s, 3F)

EXAMPLE 20: Synthesis of Compound A29



[00543] Synthesis of 6-bromo-3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine

[00544] To a solution of 6,8-dibromo-3-chloro-imidazo[1,2-a]pyrazine (4.5 g, 14.45 mmol, 1 eq) in THF (35 mL) were added K₂CO₃ (3.99 g, 28.91 mmol, 2 eq) and (2R)-2-(trifluoromethyl) azetidine (4.73 g, 15.90 mmol, 1.1 eq, TsOH salt). The mixture was stirred at 60°C for 4 hrs. TLC showed starting material was consumed and a new product was detected. After cooling to room temperature, the reaction mixture was diluted with water (30 mL) and concentrated under reduced pressure to remove the organic solvent. The residue was extracted with ethyl acetate (25 mL × 3). The organic layers were washed with brine (25 mL × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 10:1 to 5:1 (TLC: petroleum ether:ethyl acetate = 5:1, R_f = 0.3) to give 6-bromo-3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (4.2 g, yield 78.44%) as a white solid.

[00545] ¹H NMR (400 MHz, CDCl₃-d) δ 7.64 (s, 1 H), 7.47 (s, 1 H), 5.23 (dt, J = 9.16, 5.80 Hz, 1 H), 4.76 (td, J = 8.82, 6.63 Hz, 1 H), 4.56 (td, J = 9.35, 5.94 Hz, 1 H), 2.68 - 2.80 (m, 1 H), 2.53 - 2.66 (m, 1 H)

[00546] Synthesis of tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate

[00547] To a mixture of 6-bromo-3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazine (4.2 g, 11.81 mmol, 1 eq) and tert-butyl 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetyl]piperazine-1-carboxylate (5.46 g, 12.99 mmol, 1.1 eq) in a mixture of H₂O (7 mL) and dioxane (35 mL) were added Pd(dppf)Cl₂ (1.19 g, 1.62 mmol, 0.1 eq) and Na₂CO₃ (3.76 g, 35.44 mmol, 3 eq). The mixture was stirred at 80°C for 12 hrs. TLC indicated one major new product was detected. The reaction mixture was concentrated under reduced pressure to remove the organic solvent. The residue was diluted with water (50 mL) and extracted with ethyl acetate (30 mL × 2). The organic layers were washed with brine (35 mL × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 1:1 to 3:2 (TLC: petroleum ether:ethyl acetate = 1:2, R_f = 0.5) to give tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate (3.2 g, yield 47.62%) as a white solid.

[00548] ¹H NMR (400 MHz, CDCl₃-d) δ 7.97 (s, 1 H), 7.92 (s, 1 H), 7.68 (s, 1 H), 7.48 (s, 1 H), 5.19 (br d, J = 7.25 Hz, 1 H), 4.97 - 5.12 (m, 2 H), 4.75 (br d, J = 6.75 Hz, 1 H), 4.50 - 4.66 (m, 1 H), 3.52 - 3.70 (m, 4 H), 3.32 - 3.49 (m, 4 H), 2.66 (br d, J = 6.88 Hz, 2 H), 1.48 (s, 9 H)

[00549] Synthesis of (R)-2-(4-(3-chloro-8-(2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(piperazin-1-yl)ethan-1-one

[00550] To a solution of tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate (3.2 g, 5.34 mmol, 1 eq) in DCM (25.6 mL) and was added TFA (6.4 mL). The mixture was stirred at 20°C for 1 hr. TLC indicated starting material was consumed and one new product was detected. The reaction mixture was concentrated under reduced pressure, diluted with water (50 mL) and basified with aq. ammonium hydroxide to pH = 9. The solid was collected by filtration and triturated with ethyl acetate (50 mL). The crude product was diluted with MeOH (200 mL) and basic free resin was added to the solution to pH = 9, the mixture was filtered and the solid was collected and dried under reduced pressure to give 2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-piperazin-1-yl-ethanone (1.5 g, 3.04 mmol, 53.98% yield, 95% purity) as a white solid.

[00551] The solid was dissolved in IPA (10 mL), succinic acid (755.58 mg, 6.40 mmol, 2 eq) was added, and the mixture was stirred at 75°C for 2 hrs. After cooling to room temperature and standing for 10 hrs, the reaction mixture was filtered and the filter cake was dried under reduced pressure to give a residue, which was triturated with IPA (10 mL) to give 2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-piperazin-1-yl-ethanone (1.27 g, yield 80.24%, succinic acid salt) as a white solid.

[00552] LCMS (ESI+): m/z 469.2 (M+H)⁺, RT: 1.885 min (Method P)

[00554] ¹⁹F NMR (400 MHz, MeOD-d₄) δ -77.82 (s, 3F)

Nc1cc(C(F)(F)F)nc(Br)n1
 $\xrightarrow[\text{Py (2.5 eq)}]{\text{Br}_2 \text{ (2.5 eq)}}$
 $\xrightarrow[\text{20}^\circ\text{C, 12 h}]{\text{DCM (10 V)}}$
Nc1c(Br)nc(C(F)(F)F)n1
 $\xrightarrow[\text{H}_2\text{O:IPA (5:1, 60 V)}]{\text{(chloromethyl)oxirane (3 eq)}}$
 $\xrightarrow[\text{110}^\circ\text{C, 4 h}]{\text{H}_2\text{O:IPA (5:1, 60 V)}}$
Nc1c(Br)nc(C(F)(F)F)n1C2OC2
 $\xrightarrow[\text{THF/H}_2\text{O (5/1, 10 V)}]{\text{Sphos Pd G2 (0.1 eq), K}_2\text{PO}_4 \text{ (2 eq)}}$
 $\xrightarrow[\text{80}^\circ\text{C, 2 h}]{\text{THF/H}_2\text{O (5/1, 10 V)}}$
Nc1c(Br)nc(C(F)(F)F)n1C2OC2C3=NC4=CC(=CC=C4C(F)(F)F)N=C3N5CCN(CC5)C(=O)N6CCN(CC6)C(=O)N7C8=CC=CC=C8C(F)(F)F7
 $\xrightarrow[\text{25}^\circ\text{C, 2 h}]{\text{DCM/TFA (5/1, 10 V)}}$
Nc1c(C2OC2)nc(C(F)(F)F)n1C3=NC4=CC(=CC=C4C(F)(F)F)N=C3N5CCN(CC5)C(=O)N6CCN(CC6)C(=O)N7C8=CC=CC=C8C(F)(F)F7

[00556] To a solution of 6-(trifluoromethyl)pyrazin-2-amine (2 g, 12.26 mmol, 1 eq) in DCM (20 mL) was added pyridine (2.42 g, 30.65 mmol, 2.47 mL, 2.5 eq) and bromine (4.89 g, 30.65 mmol, 1.58 mL, 2.5 eq) at 20°C. The mixture was stirred at 20°C for 12 hrs. LCMS showed one main new peak was detected. The reaction mixture was quenched by addition of water (20 mL) and then extracted with DCM (50 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 10:1 to 5:1 (TLC: petroleum ether:ethyl acetate = 5:1, R_f = 0.68) to give 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine (2.5 g, yield 62.98%) as a pale-yellow solid.

[00559] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -64.71(s, 3F)

[00561] To a solution of 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine (2.5 g, 7.70 mmol, 1 eq) in the mixture of H₂O (120 mL) and IPA (30 mL) was added 2-chloroacetaldehyde (4.55 g, 23.14 mmol, 3.73 mL, 40% purity, 3 eq). The

mixture was stirred at 110°C for 4 hrs. LCMS showed desired compound was detected. After cooling to room temperature, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 250*50 mm*10 μm; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 30%-60% B over 10 min) to give 6,8-dibromo-5-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.3 g, yield 11.04%) as a yellow solid.

[00562] LCMS (ESI+): m/z 343.9, 345.8 (M+H, M+3) +, RT: 0.336 min (Method N)

[00563] ¹H NMR (400 MHz, DMSO-d₆) δ 8.47 (br s, 1H), 8.07 (s, 1H)

[00564] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -60.63 (s, 3F)

[00565] Synthesis of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazine

[00566] To a solution of 6,8-dibromo-5-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.28 g, 811.79 μmol, 1 eq) in THF (2.8 mL) was added K₂CO₃ (338.45 mg, 2.44 mmol, 3 eq) and (2S)-2-methylazetidine (104.79 mg, 974.15 μmol, 1.2 eq, HCl salt). The mixture was stirred at 60°C for 3 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 6:1 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.7) to give 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.21 g, yield 73.33%) as a yellow solid.

[00567] LCMS (ESI+): m/z 335.0, 336.9 (M+H, M+3)+, RT: 0.439 min (Method N)

[00568] ¹H NMR (400 MHz, DMSO-d₆) δ 7.96 (br s, 1H), 7.68 (br s, 1H), 4.84 - 4.50 (m, 2H), 4.30 - 4.06 (m, 1H), 2.71 - 2.57 (m, 1H), 2.02 (br s, 1H), 1.71 - 1.50 (m, 3H)

[00569] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -58.33 (s, 3F)

[00570] Synthesis of tert-butyl 4-[2-[4-[8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate

[00571] To a solution of 6-bromo-8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazine (0.21 g, 625.88 μmol, 1 eq) and tert-butyl 4-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetyl]piperazine-1-carboxylate (316.05 mg, 751.97 μmol, 1.2 eq) in the mixture of THF (1.75 mL) and H₂O (0.35 mL) was added K₃PO₄ (266.03 mg, 1.25 mmol, 2 eq) and Sphos Pd G2 (45.15 mg, 62.66 μmol, 0.1 eq). The mixture was stirred at 80°C for 2 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to room temperature, the reaction mixture was diluted with water (3 mL), extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column on silica gel, eluting with petroleum ether:ethyl acetate = 5:1 to 2:1 (TLC: petroleum ether:ethyl acetate = 1:2, R_f = 0.3) to give tert-butyl 4-[2-[4-[8-[(2S)-2-methylazetidin-1-yl]-5-

(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate (0.25 g, yield 62.55%) as a white solid.

[00572] LCMS (ESI+): m/z 549.1 (M+H)⁺, RT: 0.391 min (Method N)

[00573] ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 - 7.87 (m, 2H), 7.68 (s, 1H), 7.63 (s, 1H), 5.22 (s, 2H), 4.93 - 4.42 (m, 2H), 4.40 - 4.06 (m, 1H), 3.52 - 3.41 (m, 4H), 3.38 (br s, 4H), 2.69 - 2.55 (m, 1H), 2.02 (br s, 1H), 1.67 - 1.51 (m, 3H), 1.42 (s, 9H)

[00574] ¹⁹F NMR (400 MHz, DMSO-d₆) δ -58.15 (s, 3F)

[00575] Synthesis of 2-[4-[8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-piperazin-1-yl-ethanone

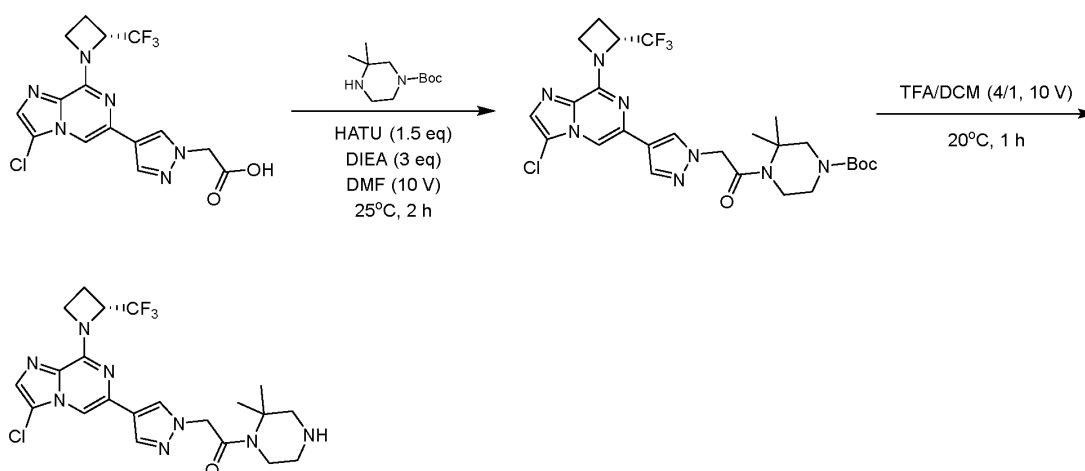
[00576] To a solution of tert-butyl 4-[2-[4-[8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]piperazine-1-carboxylate (0.25 g, 455.74 μmol, 1 eq) in DCM (2.5 mL) was added TFA (0.5 mL). The mixture was stirred at 25°C for 2 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (neutral condition, column: Phenomenex C18 150 * 25 mm * 10 μm; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 18%-48% B over 11 min) to give 2-[4-[8-[(2S)-2-methylazetidin-1-yl]-5-(trifluoromethyl)imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-piperazin-1-yl-ethanone (37 mg, yield 18.07%) as a white solid.

[00577] LCMS (ESI+): m/z 449.2 (M+H)⁺, RT: 1.691 min (Method P)

[00578] ¹H NMR (400 MHz, METHANOL-d₄) δ 7.92 (s, 1H), 7.85 (br s, 1H), 7.73 (s, 1H), 7.62 (s, 1H), 5.20 (s, 2H), 5.02 (br d, J = 1.5 Hz, 1H), 4.59 (br s, 1H), 4.51 (br d, J = 2.5 Hz, 1H), 3.61 - 3.55 (m, 4H), 2.89 - 2.85 (m, 2H), 2.84 - 2.80 (m, 2H), 2.70 - 2.60 (m, 1H), 2.14 - 2.04 (m, 1H), 1.65 (br d, J = 6.0 Hz, 3H)

[00579] ¹⁹F NMR (400 MHz, METHANOL-d₄) δ -60.41 (s, 3F)

EXAMPLE 22: Synthesis of Compound A31



[00580] Synthesis of tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]-3,3-dimethyl-piperazine-1-carboxylate

[00581] To a solution of 2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetic acid (100 mg, 224.58 μ mol, 1 eq) in DMF (1 mL) were added HATU (102.47 mg, 269.50 μ mol, 1.2 eq), tert-butyl 3,3-dimethylpiperazine-1-carboxylate (57.75 mg, 269.50 μ mol, 1.2 eq) and DIEA (87.08 mg, 673.75 μ mol, 117.35 μ L, 3 eq). The mixture was stirred at 25°C for 2 hrs. TLC indicated starting material was consumed and one major new product was detected. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (5 mL $\times$ 3). The organic layers were washed with brine (8 mL $\times$ 3), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether:ethyl acetate = 1:2, R_f = 0.5) to give tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]-3,3-dimethyl-piperazine-1-carboxylate (60 mg, yield 38.04%) as a yellow oil.

[00582] ¹H NMR (400 MHz, CDCl₃-d) δ 7.89 - 7.96 (m, 2 H), 7.69 (s, 1 H), 7.45 - 7.50 (m, 1 H), 5.19 (br d, J = 8.50 Hz, 1 H), 4.98 (s, 2 H), 4.70 - 4.84 (m, 1 H), 4.48 - 4.62 (m, 1 H), 3.57 - 3.73 (m, 2 H), 3.36 - 3.54 (m, 4 H), 2.58 - 2.71 (m, 2 H), 1.48 - 1.52 (m, 6 H), 1.47 (s, 9 H)

[00583] Synthesis of (R)-2-(4-(3-chloro-8-(2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(2,2-dimethylpiperazin-1-yl)ethan-1-one

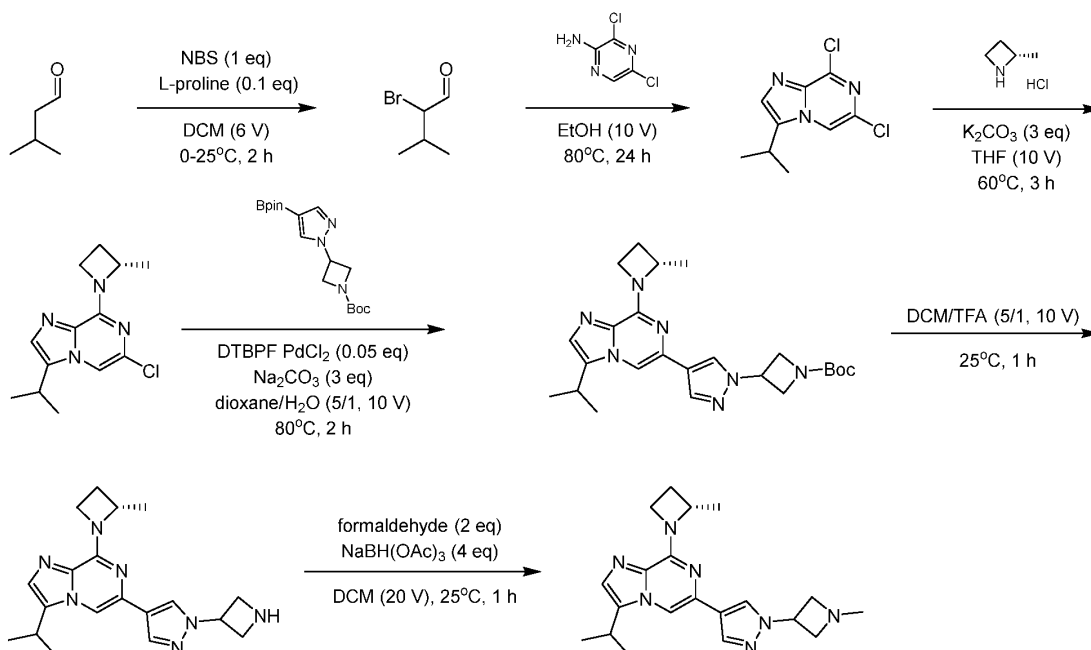
[00584] To a solution of tert-butyl 4-[2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]acetyl]-3,3-dimethyl-piperazine-1-carboxylate (60 mg, 100.50 μ mol, 1 eq) in DCM (0.5 mL) was added TFA (0.1 mL). The mixture was stirred at 20°C for 1 hr. LCMS indicated starting material was consumed and desired product was detected. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (neutral condition; column: Daisogel SP ODS RPS 150 * 25 mm * 5 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 25%-55% B over 11 min) to give 2-[4-[3-chloro-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-(2,2-dimethylpiperazin-1-yl)ethanone (15 mg, yield 29.74%) as a white solid.

[00585] LCMS (ESI+): m/z 497.3 (M+H)⁺, RT: 2.848 min (Method P)

[00586] ¹H NMR (400 MHz, MeOD-d₄) δ 8.06 (s, 1 H), 8.02 (br d, J = 3.38 Hz, 2 H), 7.54 (s, 1 H), 5.25 - 5.41 (m, 1 H), 5.12 (s, 2 H), 4.64 - 4.70 (m, 1 H), 4.51 - 4.57 (m, 1 H), 3.47 - 3.53 (m, 2 H), 2.97 (br t, J = 5.00 Hz, 2 H), 2.71 (m, 3 H), 2.55 - 2.65 (m, 1 H), 1.45 (s, 6 H)

[00587] ¹⁹F NMR (400 MHz, MeOD-d₄) δ -77.86 (s, 3F)

[00588] EXAMPLE 23: Synthesis of Compound A32



[00589] Synthesis of 2-bromo-3-methylbutanal

[00590] To a solution of 3-methylbutanal (20 g, 232.30 mmol, 38.22 mL, 1 eq) in DCM (200 mL) was added NBS (41.33 g, 232.30 mmol, 1 eq) and L-proline (2.67 g, 23.22 mmol, 0.1 eq) at 0°C. The mixture was stirred at 25°C for 2 hrs. TLC indicated starting material was consumed and one new product was formed. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether: ethyl acetate = 200:1 to 100:1 (TLC: petroleum ether:ethyl acetate = 1:0, R_f = 0.7) to give 2-bromo-3-methylbutanal (15 g, yield 39.14%) as a yellow oil.

[00591] ¹H NMR (400 MHz, CDCl₃-d) δ 9.45 (d, J = 3.88 Hz, 1 H) 4.01 - 4.10 (m, 1 H) 2.25 (q, J = 6.71 Hz, 1 H) 1.09 (t, J = 6.07 Hz, 6 H)

[00592] Synthesis of 6,8-dichloro-3-isopropylimidazo[1,2-a]pyrazine

[00593] To a solution of 2-bromo-3-methylbutanal (5.0 g, 30.30 mmol, 2 eq) in EtOH (100 mL) was added 3,5-dichloropyrazin-2-amine (2.48 g, 15.15 mmol, 1 eq). The mixture was stirred at 80°C for 24 hrs. TLC indicated starting material was consumed and one new product was formed. The mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 10:1 to 5:1 (TLC: petroleum ether:ethyl acetate = 5:1, R_f = 0.5) to give 6,8-dichloro-3-isopropyl-imidazo[1,2-a]pyrazine (2 g, yield 55.02%) as a yellow solid.

[00594] ¹H NMR (400 MHz, CDCl₃-d) δ 7.90 - 8.01 (m, 1 H) 7.51 - 7.76 (m, 1 H) 3.03 - 3.25 (m, 1 H) 1.44 (d, J = 6.88 Hz, 6 H)

[00595] Synthesis of 6-chloro-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00596] To a solution of 6,8-dichloro-3-isopropyl-imidazo[1,2-a]pyrazine (300 mg, 1.30 mmol, 1 eq) in THF (4 mL) were added (2S)-2-methylazetidine (154.29 mg, 1.43 mmol, 1.1 eq, HCl salt) and K₂CO₃ (540.58 mg, 3.91 mmol, 3 eq). The mixture was stirred at 60°C for 3 hrs. TLC indicated starting material was consumed and one new product was formed. After cooling to room temperature, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 × 3 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 5:1 to 3:1 (TLC: petroleum ether:ethyl acetate = 3:1, R_f = 0.5) to give 6-chloro-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (250 mg, yield 72.42%) as a white solid.

[00597] ¹H NMR (400 MHz, CDCl₃-d) δ 7.29 (s, 1 H) 7.23 (s, 1 H) 4.94 (br d, J = 4.75 Hz, 1 H) 4.58 (br d, J = 7.25 Hz, 1 H) 4.42 (br d, J = 6.38 Hz, 1 H) 2.98 - 3.14 (m, 1 H) 2.55 - 2.71 (m, 1 H) 2.05 (ddd, J = 11.16, 5.60, 3.25 Hz, 1 H) 1.66 (d, J = 6.25 Hz, 3 H) 1.36 (d, J = 6.75 Hz, 6 H)

[00598] Synthesis of tert-butyl 3-[4-[3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00599] To a solution of 6-chloro-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (250 mg, 944.28 μmol, 1 eq) in dioxane (4 mL) and water (0.8 mL) were added tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (395.73 mg, 1.13 mmol, 1.2 eq), Pd(dppf)Cl₂ (69.09 mg, 94.43 μmol, 0.1 eq) and Na₂CO₃ (300.25 mg, 2.83 mmol, 3 eq). The mixture was stirred at 80°C for 2 hrs under nitrogen. TLC indicated starting material was consumed and one new product was formed. The mixture was diluted with water (8 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 3:1 to 1:1 (TLC: petroleum ether:ethyl acetate = 1:1, R_f = 0.5) to give tert-butyl 3-[4-[3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (250 mg, yield 58.63%) as a white solid.

[00600] ¹H NMR (400 MHz, CDCl₃-d) δ 7.94 (s, 1 H) 7.90 (s, 1 H) 7.42 (s, 1 H) 7.29 (s, 1 H) 5.03 - 5.15 (m, 1 H) 4.87 - 4.98 (m, 1 H) 4.55 - 4.66 (m, 1 H) 4.34 - 4.43 (m, 4 H) 3.15 (dt, J = 13.63, 6.82 Hz, 1 H) 2.51 - 2.65 (m, 1 H) 2.09 (br dd, J = 9.19, 5.07 Hz, 1 H) 1.95 (br s, 1 H) 1.68 (d, J = 6.13 Hz, 3 H) 1.45 - 1.49 (m, 9 H) 1.39 (dd, J = 6.69, 3.19 Hz, 6 H)

[00601] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00602] To a solution of tert-butyl 3-[4-[3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (250 mg, 553.63 μmol, 1 eq) in DCM (3 mL) was added TFA (767.50 mg, 6.73 mmol, 500.00 μL, 12.16 eq). The resulting mixture was stirred at 25°C for 1 hr. TLC indicated starting material was consumed and one major new product was detected. The mixture was concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (200 mg, yield 68.30%) as a yellow oil, which was used for the next step without purification.

[00603] ^1H NMR (400 MHz, CDCl_3 -d) δ 8.17 (s, 1 H) 7.88 (s, 1 H) 7.58 (s, 1 H) 7.26 (s, 1 H) 5.54 - 5.77 (m, 2 H) 5.37 - 5.49 (m, 1 H) 4.58 - 4.79 (m, 6 H) 3.13 - 3.24 (m, 1 H) 2.90 (br t, J = 8.50 Hz, 1 H) 2.16 - 2.27 (m, 1 H) 1.80 (d, J = 6.25 Hz, 3 H) 1.43 (dd, J = 6.88, 2.38 Hz, 6 H)

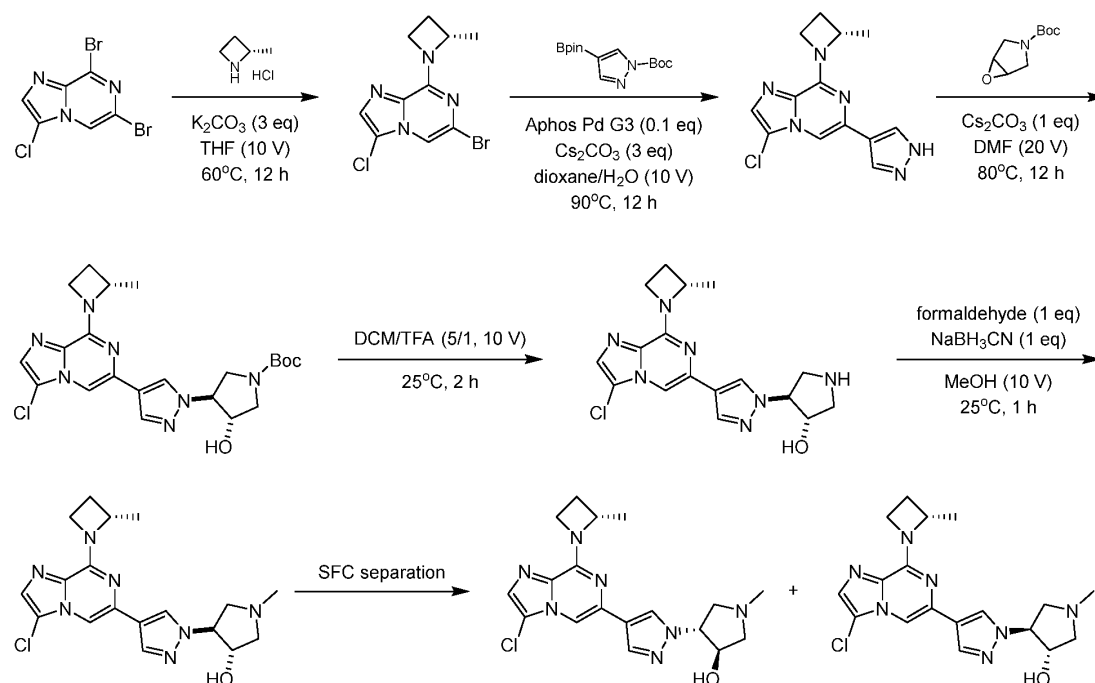
[00604] Synthesis of 3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine

[00605] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (200 mg, 378.11 μmol , 1 eq) in DCM (4 mL) was added formaldehyde (61.37 mg, 756.22 μmol , 56.30 μL , 37% purity, 2 eq) and $\text{NaBH}(\text{OAc})_3$ (320.55 mg, 1.51 mmol, 4 eq). The resulting mixture was stirred at 25°C for 1 hr. LCMS showed starting material was consumed and one new peak with desired mass was detected. The residue was purified by prep-HPLC (neutral condition. column: Daisogel SP ODS RPS 150*25mm*5 μm ; mobile phase: [water(NH_4HCO_3)-ACN]; gradient: 30%-60% B over 10 min) to give 3-isopropyl-8-[(2S)-2-methylazetidin-1-yl]-6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]imidazo[1,2-a]pyrazine (55 mg, yield 39.80%) as a white solid.

[00606] LCMS (ESI+): m/z 366.3 ($\text{M}+\text{H}$)+, RT: 1.993 min (Method O)

[00607] ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 8.19 (s, 1 H) 8.02 (s, 1 H) 7.82 (s, 1 H) 7.28 (s, 1 H) 5.05 (t, J = 7.07 Hz, 1 H) 4.88 - 4.93 (m, 1 H) 4.55 - 4.61 (m, 1 H) 4.26 - 4.41 (m, 1 H) 3.83 - 3.99 (m, 2 H) 3.64 (t, J = 7.69 Hz, 2 H) 3.28 (br d, J = 7.00 Hz, 1 H) 2.51 - 2.68 (m, 1 H) 2.49 (s, 3 H) 2.09 (br s, 1 H) 1.63 (d, J = 6.13 Hz, 3 H) 1.40 (dd, J = 6.75, 2.75 Hz, 6 H)

[00608] EXAMPLE 24: Synthesis of Compound A33 and A34



[00609] Synthesis of 6-bromo-3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00610] To a solution of 6,8-dibromo-3-chloro-imidazo[1,2-a]pyrazine (1 g, 3.21 mmol, 1 eq) in THF (10 mL) was added K₂CO₃ (1.33 g, 9.64 mmol, 3 eq) and (2S)-2-methylazetidine (380.07 mg, 3.53 mmol, 1.1 eq, HCl salt). The mixture was stirred at 60°C for 12 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to 20°C, the residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 6-bromo-3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (900 mg, yield 92.92%) as a yellow solid, which was used for the next step without purification.

[00611] LCMS (ESI+): m/z 301.0, 302.9 (M+H, M+3)+, RT: 0.470 min (Method N)

[00612] ¹H NMR (400 MHz, DMSO-d₆) δ 7.72 (s, 1H), 7.6-7.7 (m, 1H), 4.79 (br d, 1H, J = 1.0 Hz), 4.1-4.5 (m, 2H), 2.56 (br s, 1H), 2.0-2.1 (m, 1H), 1.55 (br d, 3H, J = 4.0 Hz)

[00613] Synthesis of 3-chloro-6-(1H-pyrazol-4-yl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine

[00614] To a solution of 6-bromo-3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (500 mg, 1.66 mmol, 1 eq) in a mixture of dioxane (5 mL) and H₂O (0.5 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate (585.25 mg, 1.99 mmol, 1.2 eq), Cs₂CO₃ (1.62 g, 4.98 mmol, 3 eq) and APhos Pd G3 (105.30 mg, 165.80 μmol, 0.1 eq). The mixture was stirred at 90°C for 12 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to 20°C, the residue was diluted with water (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 3:1 to 1:1 (TLC: petroleum ether:ethyl acetate = 1:1, R_f = 0.5) to give 3-chloro-6-(1H-pyrazol-4-yl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (300 mg, yield 62.67%) as a pale-yellow solid.

[00615] LCMS (ESI+): m/z 289.0 (M+H)+, RT: 0.290 min (Method N)

[00616] ¹H NMR (400 MHz, DMSO-d₆) δ 12.95 (br s, 1H), 8.20 (br s, 1H), 8.01 (br s, 1H), 7.93 (s, 1H), 7.5-7.7 (m, 1H), 4.81 (br d, 1H, J = 5.8 Hz), 4.3-4.5 (m, 2H), 2.56 (br s, 1H), 2.0-2.1 (m, 1H), 1.62 (d, 3H, J = 6.1 Hz)

[00617] Synthesis of trans-tert-butyl 3-[4-[3-chloro-8-(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-4-hydroxy-pyrrolidine-1-carboxylate

[00618] To a solution of 3-chloro-6-(1H-pyrazol-4-yl)-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazine (300 mg, 1.04 mmol, 1 eq) in DMF (6 mL) was added Cs₂CO₃ (388.53 mg, 1.04 mmol, 1 eq) and tert-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (192.44 mg, 1.04 mmol, 1 eq). The mixture was stirred at 80°C for 12 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. After cooling to 20°C, the reaction mixture was poured into water (30 mL), the solid was collected by filtration and dried in vacuo to give trans-tert-butyl 3-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-4-hydroxy-pyrrolidine-1-carboxylate (340 mg, yield 69.04%) as a pale-yellow solid, which was used for the next step without purification.

[00619] LCMS (ESI+): m/z 474.2 (M+H)⁺, RT: 0.408 min (Method N)

[00620] ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (s, 1H), 8.04 (s, 1H), 7.93 (s, 1H), 7.62 (s, 1H), 5.4-6.1 (m, 1H), 4.7-4.8 (m, 2H), 4.3-4.5 (m, 3H), 3.8-3.9 (m, 1H), 3.62 (dt, 2H, J = 5.1, 12.1 Hz), 3.1-3.2 (m, 1H), 2.5-2.6 (m, 1H), 2.0-2.1 (m, 1H), 1.61 (d, 3H, J = 6.1 Hz), 1.42 (s, 9H)

[00621] Synthesis of trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidin-3-ol

[00622] To a solution of trans-tert-butyl 3-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-4-hydroxy-pyrrolidine-1-carboxylate (400.00 mg, 0.85 mmol, 1 eq) in DCM (3.33 mL) was added TFA (0.7 mL). The mixture was stirred at 25°C for 2 hrs. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure, diluted with acetonitrile (10 mL) and basified by addition of basic free resin to pH = 9, filtered and concentrated under reduced pressure to give trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidin-3-ol (290 mg, yield 91.92%) as a white solid, which was used for the next step without purification.

[00623] LCMS (ESI+): m/z 374.1 (M+H)⁺, RT: 0.251 min (Method N)

[00624] ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 1H), 7.97 (s, 1H), 7.91 (s, 1H), 7.62 (s, 1H), 5.29 (br s, 1H), 4.79 (br d, 1H, J = 4.9 Hz), 4.5-4.6 (m, 1H), 4.41 (br s, 1H), 4.31 (br s, 2H), 3.36 (br s, 2H), 3.13 (dd, 1H, J = 5.8, 11.7 Hz), 3.0-3.1 (m, 1H), 2.70 (dd, 1H, J = 3.9, 11.7 Hz), 2.5-2.6 (m, 1H), 2.0-2.1 (m, 1H), 1.61 (d, 3H, J = 6.1 Hz)

[00625] Synthesis of trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-methyl-pyrrolidin-3-ol

[00626] To a solution of trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]pyrrolidin-3-ol (290.00 mg, 0.78 mmol, 1 eq) in MeOH (2.9 mL) was added formaldehyde (62.95 mg, 0.78 mmol, 57.76 μL, 37% purity, 1 eq) and NaBH₃CN (48.74 mg, 0.78 mmol, 1 eq). The mixture was stirred at 25°C for 1 hr. LCMS showed starting material was consumed and one new peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition, column: CD19-Daisogel SP-100-8-ODS-PK 200 * 50 * 10 μm; mobile phase: [water (NH₄HCO₃)-ACN]; gradient: 35%-65% B over 11 min) to give trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-methyl-pyrrolidin-3-ol (180 mg, yield 59.82%) as a white solid.

[00627] LCMS (ESI+): m/z 388.3 (M+H)⁺, RT: 2.091 min (Method O)

[00628] ¹H NMR (400 MHz METHANOL-d₄) δ 8.17 (s, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.44 (s, 1H), 4.9-4.9 (m, 1H), 4.69 (dt, 1H, J = 4.1, 7.1 Hz), 4.5-4.6 (m, 2H), 4.3-4.4 (m, 1H), 3.2-3.2 (m, 1H), 3.05 (dd, 1H, J = 6.7, 10.1 Hz), 2.9-3.0 (m, 1H), 2.67 (dd, 1H, J = 4.6, 10.1 Hz), 2.6-2.6 (m, 1H), 2.41 (s, 3H), 2.0-2.2 (m, 1H), 1.65 (d, 3H, J = 6.1 Hz)

[00629] Synthesis of (3R,4R)-4-[4-[3-chloro-8-[(S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]-1H-pyrazol-1-yl]-1-methylpyrrolidin-3-ol and (3S,4S)-4-[4-[3-chloro-8-[(S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-methyl-pyrrolidin-3-ol

[00630] Trans-4-[4-[3-chloro-8-[(2S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-methylpyrrolidin-3-ol (186.75 mg, 481.49 μ mol, 1 eq) was separated by SFC (base condition, column: DAICEL CHIRALPAK IC(250 mm * 30 mm, 10 μ m); mobile phase: [CO₂-EtOH (0.1% NH₃/H₂O)]; to give (3R,4R)-4-[4-(3-chloro-8-[(S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl]-1-methylpyrrolidin-3-ol (40 mg, yield 21.20%, absolute stereochemistry not determined and randomly assigned, P1) as a white solid and (3S,4S)-4-[4-[3-chloro-8-[(S)-2-methylazetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl]pyrazol-1-yl]-1-methylpyrrolidin-3-ol (39 mg, yield 20.67%, absolute stereochemistry not determined and randomly assigned, P2) as a white solid.

[00631] Example A33

[00632] LCMS (ESI+): m/z 388.2 (M+H)⁺, RT: 2.115 min (Method O)

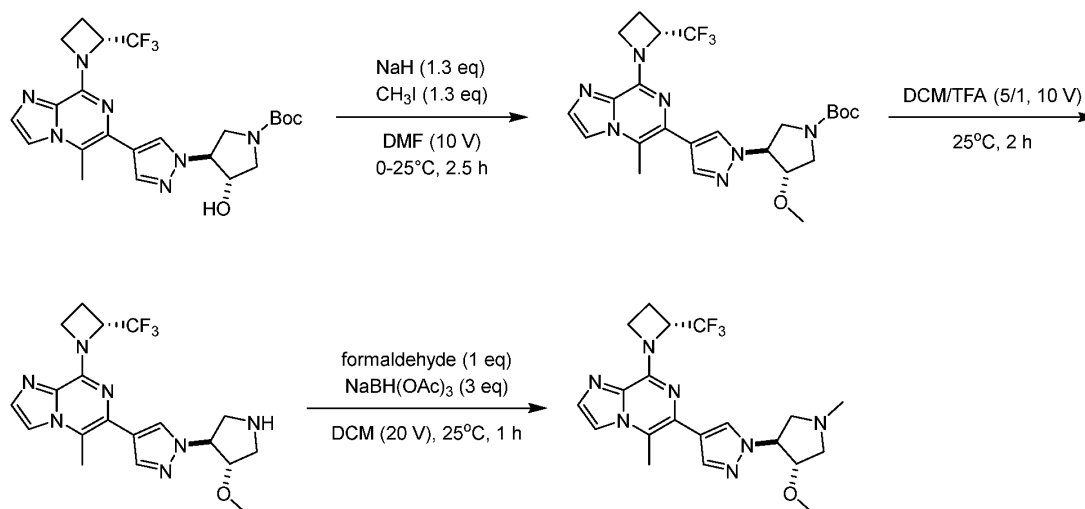
[00633] ¹H NMR (M400 MHz, ETHANOL-d₄) δ 8.18 (s, 1H), 7.97 (s, 1H), 7.79 (s, 1H), 7.45 (d, 1H, J = 1.1 Hz), 4.9-4.9 (m, 1H), 4.7-4.7 (m, 1H), 4.5-4.6 (m, 2H), 4.3-4.4 (m, 1H), 3.20 (br t, 1H, J = 9.1 Hz), 3.05 (dd, 1H, J = 6.7, 9.9 Hz), 2.95 (dd, 1H, J = 6.6, 9.9 Hz), 2.68 (br dd, 1H, J = 4.4, 9.9 Hz), 2.6-2.6 (m, 1H), 2.41 (s, 3H), 2.0-2.2 (m, 1H), 1.65 (d, 3H, J = 6.1 Hz)

[00634] Example A34

[00635] LCMS (ESI+): m/z 388.3 (M+H)⁺, RT: 2.106 min (Method B)

[00636] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.18 (s, 1H), 7.97 (s, 1H), 7.79 (s, 1H), 7.45 (s, 1H), 4.9-4.9 (m, 1H), 4.7-4.7 (m, 1H), 4.5-4.6 (m, 2H), 4.3-4.4 (m, 1H), 3.1-3.2 (m, 1H), 3.05 (dd, 1H, J = 6.8, 10.0 Hz), 2.95 (dd, 1H, J = 6.4, 10.1 Hz), 2.67 (dd, 1H, J = 4.6, 10.1 Hz), 2.6-2.6 (m, 1H), 2.41 (s, 3H), 2.0-2.2 (m, 1H), 1.65 (d, 3H, J = 6.3 Hz)

[00637] EXAMPLE 25: Synthesis of Compound A35



[00638] Synthesis of tert-butyl (rac-trans)-3-methoxy-4-(4-(5-methyl-8-[(R)-2-(trifluoromethyl)azetidin-1-yl]imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate

[00639] To a solution of tert-butyl (rac-trans)-3-hydroxy-4-(4-(5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (250 mg, 492.59 μ mol, 1 eq) in DMF (2.5 mL) was added NaH (15.37 mg, 640.37 μ mol, 60% purity, 1.3 eq) at 0°C and stirred for 30 minutes, then iodomethane (90.89 mg, 640.37 μ mol, 1.3 eq) was added slowly. The mixture was stirred at 25°C for 2 hrs. LCMS showed the starting material was consumed and desired mass was detected. The reaction mixture was poured into excess aq. saturated ammonium chloride and extracted with ethyl acetate (15 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl (rac-trans)-3-methoxy-4-(4-(5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (220 mg, yield 79.64 %) as a white solid, which was used for the next step without purification.

[00640] LCMS (ESI+): m/z 522.2 (M+H)⁺, RT: 0.440 min (Method N)

[00641] ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (s, 1 H), 8.01 (d, J = 1.00 Hz, 1 H), 7.88 (d, J = 1.75 Hz, 1 H), 7.65 (d, J = 1.00 Hz, 1 H), 5.18 - 5.31 (m, 1 H), 4.99 (br s, 1 H), 4.36 - 4.55 (m, 2 H), 4.18 (br s, 1 H), 3.75 - 3.82 (m, 1 H), 3.62 - 3.72 (m, 2 H), 3.30 (d, J = 2.13 Hz, 3 H), 2.63 - 2.69 (m, 1 H), 2.61 (s, 3 H), 2.43 - 2.50 (m, 2 H), 1.41 (br d, J = 4.13 Hz, 9 H)

[00642] Synthesis of 6-(1-((rac-trans)-4-methoxypyrrolidin-3-yl)-1H-pyrazol-4-yl)-5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazine

[00643] To a solution of tert-butyl (rac-trans)-3-methoxy-4-(4-(5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazin-6-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (220 mg, 421.82 μ mol, 1 eq) in DCM (2.5 mL) was added TFA (0.5 mL). The mixture was stirred at 25°C for 2 hrs. LCMS showed the starting material was consumed and desired mass was detected. The mixture was concentrated under reduced pressure to give 6-(1-((rac-trans)-4-methoxypyrrolidin-3-yl)-1H-pyrazol-4-yl)-5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazine (160 mg, yield 87.30%) as a yellow oil, which was used for the next step without purification.

[00644] LCMS (ESI+): m/z 422.2 (M+H)⁺, RT: 0.395 min (Method N)

[00645] Synthesis of 6-(1-((rac-trans)-4-methoxy-1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazine

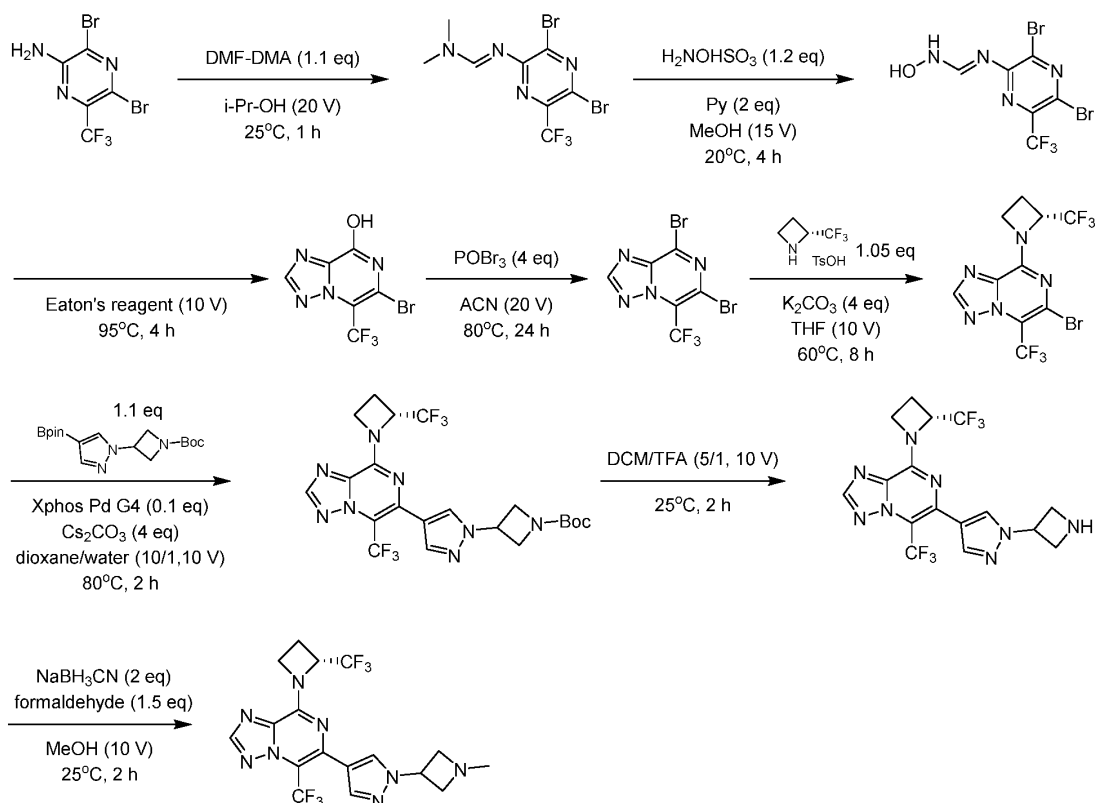
[00646] To a solution of 6-(1-((rac-trans)-4-methoxypyrrolidin-3-yl)-1H-pyrazol-4-yl)-5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazine (180 mg, 427.12 μ mol, 1 eq) and formaldehyde (34.66 mg, 427.12 mmol, purity 37%, 1 eq) in DCM (3.6 mL) was added NaBH(OAc)₃ (271.57 mg, 1.28 mmol, 3 eq). The mixture was stirred at 25°C for 1 hr. LCMS showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition, column: CD07-Daisogel SP-100-8-ODS-PK 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water(NH₄HCO₃)-ACN]; gradient: 33%-63% B over 10 min) to afford 6-(1-((rac-trans)-4-methoxy-1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)-5-methyl-8-((R)-2-(trifluoromethyl)azetidin-1-yl)imidazo[1,2-a]pyrazine (70 mg, yield 52.70%) as a white solid.

[00647] LCMS (ESI+): m/z 436.4 (M+H)⁺, RT: 1.856 min (Method P)

[00648] ¹H NMR (400 MHz, METHANOL-d₄) δ 8.11 (s, 1 H), 7.88 (d, J = 15.26 Hz, 2 H), 7.63 (s, 1 H), 5.18 - 5.32 (m, 1 H), 4.82 (br s, 1 H), 4.66 (br d, J = 5.75 Hz, 1 H), 4.39 (br d, J = 8.00 Hz, 1 H), 4.17 - 4.25 (m, 1 H), 3.35 (d, J = 1.38 Hz, 3 H), 3.23 (br t, J = 8.94 Hz, 1 H), 3.00 (dd, J = 10.38, 6.63 Hz, 1 H), 2.89 (dd, J = 9.88, 6.88 Hz, 1 H), 2.81 (dd, J = 10.38, 3.13 Hz, 1 H), 2.67 (s, 3 H), 2.41 (s, 3 H), 2.54 - 2.66 (m, 2 H),

[00649] ¹⁹F NMR (400 MHz, METHANOL-d₄) δ -77.99 (s, 3F)

[00650] EXAMPLE 26: Synthesis of Compound A36



[00651] Synthesis of N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N,N-dimethyl-formamidine

[00652] To a solution of 3,5-dibromo-6-(trifluoromethyl)pyrazin-2-amine (5 g, 15.58 mmol, 1 eq) in IPA (50 mL) was added DMF-DMA (1.86 g, 15.58 mmol, 2.07 mL, 1 eq) slowly. The reaction mixture was stirred at 20°C for 1 hr. TLC indicated starting material was consumed and one major new product was detected. The mixture was filtered and the filter cake was dried under reduced pressure to give N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N,N-dimethyl-formamidine (2.3 g, yield 39.26%) as a white solid, which was used for the next step without purification.

[00653] ¹H NMR (400 MHz, CDCl₃-d) δ 8.50 (s, 1 H) 3.23 (d, J = 4.63 Hz, 6 H)

[00654] Synthesis of N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N-hydroxy-formamidine

[00655] To a solution of N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N,N-dimethyl-formamidine (1.3 g, 3.46 mmol, 1 eq) in MeOH (10 mL) were added pyridine (547.2 mg, 6.92 mmol, 2 eq) and amino hydrogen sulfate (469.22 mg, 4.15

mmol, 1.2 eq). The mixture was stirred at 20°C for 4 hrs. LCMS showed starting material was consumed and desired compound was detected. The mixture was concentrated under reduced pressure at 30°C and the residue was purified by triturating with ethyl acetate (5 mL) to give N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N-hydroxy-formamidine (0.7 g, yield 55.26%) as a white solid.

[00656] LCMS (ESI+): m/z 364.9 (M+H)+, RT: 0.377 min (Method N)

[00657] ¹H NMR (400 MHz, CDCl₃-d) δ 8.78 (br d, J = 4.88 Hz, 1 H) 7.52 - 7.77 (m, 1 H) 7.89 - 8.19 (m, 1 H)

[00658] Synthesis of 6-bromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazin-8-ol

[00659] A mixture of N'-[3,5-dibromo-6-(trifluoromethyl)pyrazin-2-yl]-N-hydroxy-formamidine (0.7 g, 1.925 mmol, 1 eq) and Eaton's reagent (7 mL) was stirred at 95°C for 4 hrs. LCMS showed starting material was consumed and product with desired mass was detected. After cooling to room temperature, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel, eluting with petroleum ether:ethyl acetate = 1:3 to 1:2 (TLC: petroleum ether:ethyl acetate = 1:2, R_f = 0.2) to give 6-bromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazin-8-ol (0.32 g, yield 58.85%) as a white solid.

[00660] LCMS (ESI+): m/z 282.9 (M+H)+, RT: 0.255 min (Method N)

[00661] ¹H NMR (400 MHz, DMSO-d₆) δ 8.23 (s, 1 H)

[00662] Synthesis of 6,8-dibromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazine

[00663] To a solution of 6-bromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazin-8-ol (200 mg, 0.71 mmol, 1 eq) in ACN (8 mL) was added POBr₃ (405.50 mg, 1.41 mmol, 2 eq) slowly, and the resulting reaction mixture was stirred at 80°C for 24 hrs. LCMS showed starting material was consumed and desired compound was detected. After cooling to room temperature, the reaction mixture was poured into iced-water (20 mL) slowly, and then extracted with ethyl acetate (10 mL × 3). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give 6,8-dibromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazine (210 mg, yield 68.70 %) as a yellow solid, which was used for the next step without purification.

[00664] LCMS (ESI+): m/z 346.9 (M+H)+, RT: 0.378 min (Method N)

[00665] ¹H NMR (400 MHz, CDCl₃-d) δ 8.61 (s, 1 H)

[00666] Synthesis of 6-bromo-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine

[00667] To a solution of 6,8-dibromo-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrazine (210 mg, 607.09 μmol, 1 eq) in THF (6 mL) were added K₂CO₃ (479.48 mg, 3.47 mmol, 3 eq) and (2R)-2-(trifluoromethyl)azetidine (378.17 mg, 1.27 mmol, 1.1 eq). The resulting reaction mixture was stirred at 60°C for 8 hrs. TLC indicated starting material was consumed and a new product was detected. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 2 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (TLC: petroleum ether:ethyl acetate = 2:1, R_f = 0.6) to give

6-bromo-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (200 mg, yield 88.67%) as a white solid.

[00668] ¹H NMR (400 MHz, CDCl₃-d) δ 8.38 (s, 1 H) 5.08 - 5.40 (m, 1 H) 4.55 - 4.92 (m, 2 H) 2.77 - 3.01 (m, 1 H) 2.54 - 2.74 (m, 1 H)

[00669] Synthesis of tert-butyl 3-[4-[5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate

[00670] To a mixture of 6-bromo-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (200 mg, 512.71 μmol, 1 eq) and tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]azetidine-1-carboxylate (196.96 mg, 563.98 μmol, 1.1 eq) in dioxane (3 mL) and water (0.3 mL) were added Cs₂CO₃ (766.77 mg, 2.35 mmol, 3 eq) and Xphos Pd G4 (67.50 mg, 78.44 μmol, 0.1 eq). The resulting mixture was stirred at 80°C for 2 hrs under a nitrogen atmosphere. LCMS showed starting material was consumed and desired product was detected. After cooling to room temperature, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 8 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 1/1, R_f = 0.3) to give tert-butyl 3-[4-[5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (200 mg, yield 73.26 %) as a yellow oil.

[00671] LCMS (ESI+): m/z 447.1 (M-55)+, RT: 0.498 min (Method N)

[00672] ¹H NMR (400 MHz, CDCl₃-d) δ 8.39 (s, 1 H) 7.76 - 7.98 (m, 2 H) 5.22 (br d, J = 2.50 Hz, 1 H) 5.02 - 5.14 (m, 1 H) 4.56 - 4.95 (m, 2 H) 4.36 - 4.51 (m, 4 H) 2.54 - 2.92 (m, 2 H) 1.48 (s, 9 H)

[00673] Synthesis of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine

[00674] To a solution of tert-butyl 3-[4-[5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl]pyrazol-1-yl]azetidine-1-carboxylate (200 mg, 375.63 μmol, 1 eq) in DCM (2 mL) was added TFA (0.5 mL), the resulting mixture was stirred at 20°C for 2 hrs. TLC (petroleum ether:ethyl acetate = 0:1, R_f = 0.05) indicated starting material was consumed and one major new product was detected. The mixture was diluted with DCM (30 mL) and then concentrated under reduced pressure to give 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (160 mg, yield 90.64%) as a yellow oil, which was used for the next step without purification.

[00675] ¹H NMR (400 MHz, CDCl₃-d) δ 7.98 (s, 1 H) 8.43 (s, 1 H) 7.98 (s, 1 H) 7.88 (s, 1 H) 5.54 (br t, J = 7.13 Hz, 1 H) 5.10 - 5.29 (m, 1 H) 4.79 - 4.89 (m, 1 H) 4.71 (br s, 1 H) 3.79 - 3.86 (m, 4 H) 2.68 (br s, 2 H)

[00676] Synthesis of 6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine

[00677] To a solution of 6-[1-(azetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl)azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (160 mg, 370.09 μmol, 1 eq) and formaldehyde (74.08 mg, 740.18 μmol, 67.97 μL, 30%

purity, 2 eq) in MeOH (2 mL) was added NaBH₃CN (23.26 mg, 370.09 μ mol, 1 eq), and the resulting reaction mixture was stirred at 25°C for 2 hrs. LCMS showed starting material was consumed and new product was detected. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (neutral condition column: CD07-Daisogel SP-100-8-ODS-PK 150*25*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN] gradient: 30%-60% B over 10 min) to give 6-[1-(1-methylazetidin-3-yl)pyrazol-4-yl]-5-(trifluoromethyl)-8-[(2R)-2-(trifluoromethyl) azetidin-1-yl]-[1,2,4]triazolo[1,5-a]pyrazine (60 mg, yield 35.90%) as a white solid.

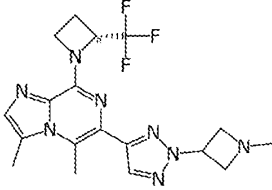
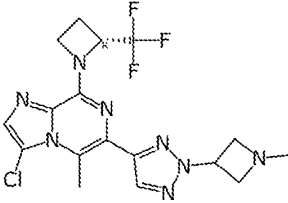
[00678] LCMS (ESI+): m/z 447.3 (M+H)⁺, RT: 2.712 min (Method O)

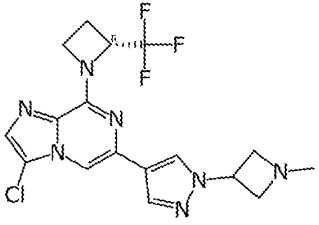
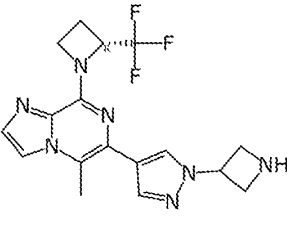
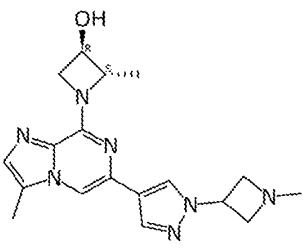
[00679] ¹H NMR (400 MHz, MeOD-d₄) δ 8.47 (s, 1 H) 8.08 (s, 1 H) 84 (s, 1 H) 5.28 - 5.44 (m, 1 H) 5.09 (t, J = 7.13 Hz, 1 H) 4.64 - 4.78 (m, 2 H) 3.88 (t, J = 8.07 Hz, 2 H) 3.57 - 3.74 (m, 2 H) 2.75 - 2.87 (m, 1 H) 2.61 (ddt, J = 11.85, 8.82, 5.99, 5.99 Hz, 1 H) 2.48 (s, 3 H)

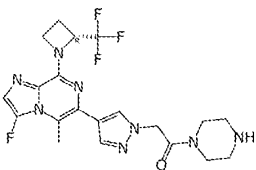
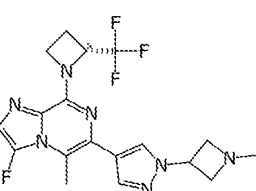
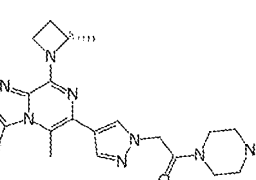
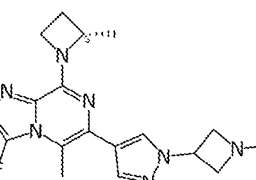
[00680] ¹⁹F NMR (400 MHz, MeOD-d₄) δ -77.68 (s, 3F) -60.50 (s, 3F)

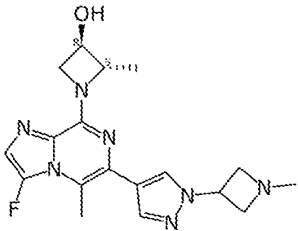
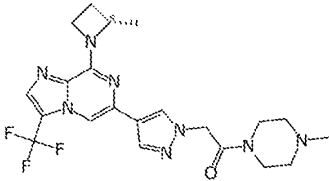
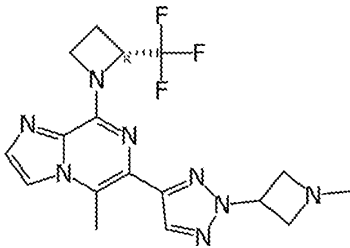
[00681] The examples in Table D were made using similar methods to those described above.

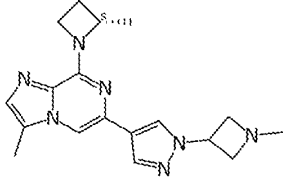
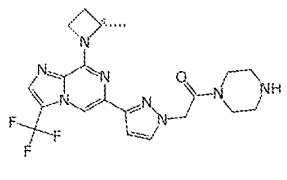
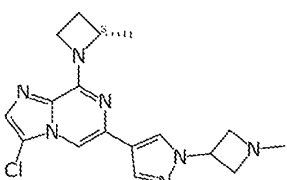
TABLE D

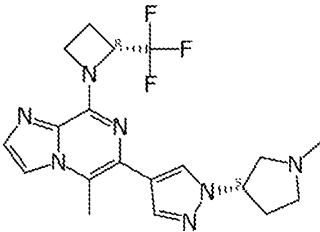
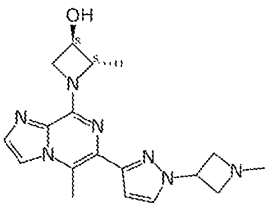
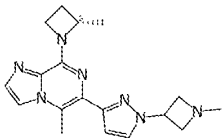
Compound number	Structure	MW	LCMS	¹ H NMR
A37		406.41	407.2 (M+H) ⁺ , RT: 1.920 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.07 (s, 1 H) 7.32 (s, 1 H) 5.28 - 5.39 (m, 1 H) 5.22 (br dd, J=14.49, 7.03 Hz, 1 H) 4.61 - 4.65 (m, 1 H) 4.29 - 4.42 (m, 1 H) 3.95 (br t, J=7.95 Hz, 2 H) 3.78 (br t, J=7.34 Hz, 2 H) 3.14 (s, 3 H) 2.83 (s, 3 H) 2.55 - 2.67 (m, 2 H) 2.50 (s, 3 H)
A38		426.83	427.1 (M+H) ⁺ , RT: 2.126 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.07 (s, 1 H) 7.51 (s, 1 H) 5.34 (br t, J=6.97 Hz, 1 H) 5.18 - 5.26 (m, 1 H) 4.60 - 4.63 (m, 1 H) 4.39 - 4.50 (m, 1 H) 3.94 (br t, J=7.83 Hz, 2 H) 3.77 (br t, J=7.34 Hz, 2 H) 3.21 (s, 3 H)

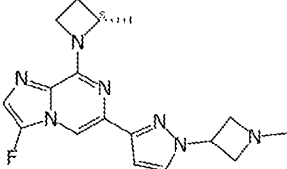
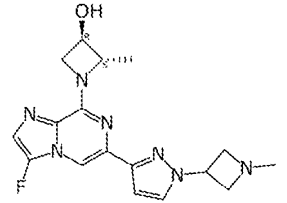
				2.55 - 2.72 (m, 2 H) 2.50 (s, 3 H)
A39		411.82	412.1 (M+H)+, RT: 2.889 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.22 (s, 1 H) 8.03 (d, J=12.76 Hz, 2 H) 7.53 (s, 1 H) 5.24 - 5.34 (m, 1 H) 5.05 (quin, J=7.06 Hz, 1 H) 4.67 (td, J=8.58, 5.96 Hz, 1 H) 4.46 - 4.57 (m, 1 H) 3.87 (br t, J=7.93 Hz, 2 H) 3.63 (br t, J=7.69 Hz, 2 H) 2.67 - 2.77 (m, 1 H) 2.56 - 2.66 (m, 1 H) 2.48 (s, 3 H)
A40		377.38	m/z 378.1 (M+H)+, RT: 1.786 min (MethoE)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.08 (s, 1 H) 8.06 (s, 1 H) 7.97 (s, 1 H) 7.75 (s, 1 H) 5.51 (quin, J=7.27 Hz, 1 H) 5.23 - 5.35 (m, 1 H) 4.68 - 4.76 (m, 1 H) 4.52 - 4.65 (m, 4 H) 4.35 - 4.45 (m, 1 H) 2.57 - 2.75 (m, 5 H)
A41		353.20	m/z 354.2 (M+H)+, RT: 2.163 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.18 (s, 1 H) 8.01 (s, 1 H) 7.82 (s, 1 H) 7.27 (d, J=0.61 Hz, 1 H) 5.05 (t, J=7.09 Hz, 1 H) 4.77 - 4.82 (m, 1 H) 4.46 - 4.56 (m, 1 H) 4.25 (dt, J=6.39, 4.75 Hz, 1 H) 4.06 (dd, J=9.48, 4.95 Hz, 1 H) 3.83 - 3.91 (m, 2 H) 3.61 - 3.67 (m, 2 H) 2.47 (d, J=6.72 Hz, 6 H) 1.63 (d, J=6.36 Hz, 3 H)

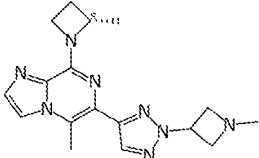
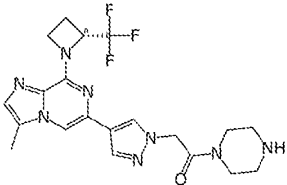
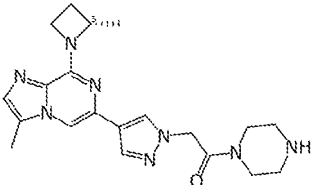
A42		466.44	m/z 467.2 (M+H) ⁺ , RT: 1.515 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 7.95 (s, 1 H) 7.88 (s, 1 H) 7.26 (d, J=6.72 Hz, 1 H) 5.27 (s, 3 H) 4.64 (td, J=8.71, 5.69 Hz, 1 H) 4.41 - 4.49 (m, 1 H) 3.88 (br s, 4 H) 3.35 (br s, 2 H) 3.27 (br s, 2 H) 2.77 (d, J=5.38 Hz, 3 H) 2.52 - 2.73 (m, 2 H)
A43		409.39	m/z 410.2 (M+1) ⁺ , RT: 1.916 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.01 (d, J=12.35 Hz, 2 H) 7.25 (d, J=6.85 Hz, 1 H) 5.39 - 5.50 (m, 1 H) 5.22 (dt, J=9.08, 6.40 Hz, 1 H) 4.89 - 4.95 (m, 1 H) 4.72 (br s, 1 H) 4.61 - 4.67 (m, 1 H) 4.46 - 4.59 (m, 2 H) 4.40 - 4.46 (m, 1 H) 2.97 - 3.26 (m, 3 H) 2.75 (d, J=5.38 Hz, 3 H) 2.51 - 2.72 (m, 2 H)
A44		412.5	m/z 413.2 (M+H) ⁺ , RT: 1.536 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 7.99 (s, 1 H) 7.78 (s, 1 H) 7.49 (d, J=6.85 Hz, 1 H) 5.35 (s, 2 H) 5.23 - 5.33 (m, 1 H) 4.67 - 4.80 (m, 1 H) 4.47 - 4.60 (m, 1 H) 3.89 (br s, 4 H) 3.38 (br s, 2 H) 3.21 - 3.28 (m, 2 H) 2.80 - 2.94 (m, 1 H) 2.53 (d, J=5.87 Hz, 3 H) 2.12 - 2.24 (m, 1 H) 1.75 (br d, J=6.24 Hz, 3 H)
A45		355.4	m/z 356.1 (M+H) ⁺ , RT: 1.582 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.06 (s, 1 H) 7.94 (s, 1 H) 7.46 (d, J=6.85 Hz, 1 H) 5.48 (br t, J=6.72 Hz, 1 H) 5.28 (br d,

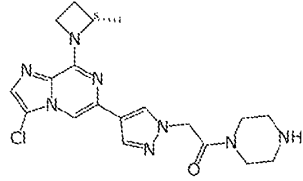
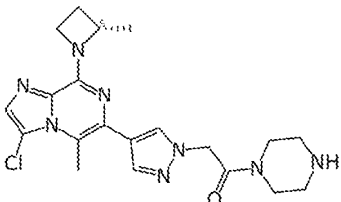
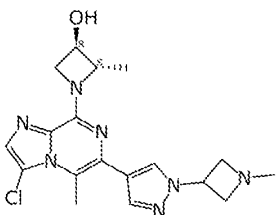
				J=4.77 Hz, 1 H) 4.67 - 4.81 (m, 2 H) 4.46 - 4.60 (m, 2 H) 3.31 (br s, 2 H) 3.16 (br s, 3 H) 2.77 - 2.95 (m, 1 H) 2.52 (d, J=5.87 Hz, 3 H) 2.11 - 2.26 (m, 1 H) 1.74 (d, J=6.36 Hz, 3 H)
A46		371.42	m/z 372.1 (M+H) ⁺ , RT: 2.27 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.01 (s, 1H) 7.85 (s, 1H), 7.18 (d, J=6.91 Hz, 1H), 5.05-5.13 (m, 1H), 4.68-4.76 (m, 1H), 4.46 (quin, J=5.75 Hz, 1H), 4.22 (dt, J=6.38, 4.80 Hz, 1H), 3.97-4.04 (m, 1H), 3.88-3.94 (m, 2H), 3.66-3.74 (m, 2H), 2.66-2.73 (m, 3H), 2.49-2.53 (m, 3H), 1.59 (d, J=6.32 Hz, 3H)
A47		462.48	m/z 463.2(M+H) ⁺ , RT: 2.774 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.10 (s, 1H), 7.96-7.98 (m, 1H), 7.87-7.90 (m, 1H), 7.84 (s, 1H), 5.18-5.21 (m, 2H), 4.59-4.63 (m, 2H), 4.39-4.47 (m, 1H), 3.63 (br t, J=5.01 Hz, 4H), 2.58-2.68 (m, 1H), 2.42-2.56 (m, 4H), 2.33 (s, 3H), 2.06-2.17 (m, 1H), 1.65-1.68 (m, 3H)
A48		392.38	m/z 393.2 (M+1) ⁺ , RT: 2.743 min (Method F)	¹ H NMR (400 MHz, CD ₃ OD, 298 K) δ (ppm) = 8.12 (s, 1H), 7.93 (s, 1H), 7.67 (s, 1H), 5.42 - 5.19 (m, 2H), 4.67 (br d, J = 5.5 Hz, 1H), 4.49 - 4.36 (m, 1H), 4.00 - 3.88 (m, 2H), 3.79 (br t, J = 7.1 Hz, 2H),

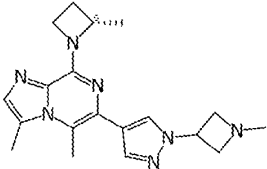
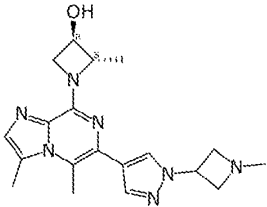
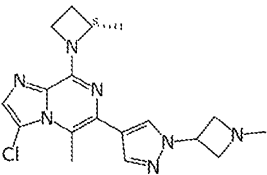
				2.94 (s, 3H), 2.72 - 2.58 (m, 2H), 2.50 (s, 3H)
A49		337.42	m/z 338.1(M+H)+, RT: 2.471 min (Method F)	¹H NMR (400 MHz, CD₃OD, 298 K) δ (ppm) = 8.17 (s, 1H), 8.01 (s, 1H), 7.78 (s, 1H), 7.26 (d, J = 0.8 Hz, 1H), 5.12 - 4.99 (m, 1H), 4.93 - 4.87 (m, 1H), 4.62 - 4.50 (m, 1H), 4.34 (dt, J = 7.0, 9.0 Hz, 1H), 3.94 - 3.82 (m, 2H), 3.63 (t, J = 7.7 Hz, 2H), 2.67 - 2.52 (m, 1H), 2.50 - 2.47 (m, 3H), 2.47 - 2.45 (m, 3H), 2.14 - 2.02 (m, 1H), 1.62 (d, J = 6.2 Hz, 3H)
A50		448.44	m/z 449.0 (M+H)+, RT: 2.683 min (Method F)	¹H NMR (400 MHz, METHANOL-d₄) δ 8.04 (s, 1 H) 7.87 (s, 1 H) 7.77 (s, 1 H) 7.57 (s, 1 H) 5.08 (t, J=7.15 Hz, 1 H) 4.79 - 4.87 (m, 1 H) 4.53 (td, J=8.76, 5.48 Hz, 1 H) 4.21 - 4.35 (m, 1 H) 3.82 - 3.99 (m, 2 H) 3.56 - 3.74 (m, 2 H) 2.59 (s, 3 H) 2.49 (s, 3 H) 1.97 - 2.13 (m, 1 H) 1.58 (d, J=6.08 Hz, 3 H)
A51		357.85	m/z 358.1 (M+H)+, RT: 1.833 min (Method I)	¹H NMR (400 MHz, DMSO-d₆) δ = 8.33 (s, 1H), 8.02 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 4.98 (quin, J = 6.9 Hz, 1H), 4.80 (br dd, J = 5.4, 7.5 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.37 - 4.27 (m, 1H), 3.70 (t, J = 7.5 Hz, 2H), 3.38 (t, J = 7.2 Hz,

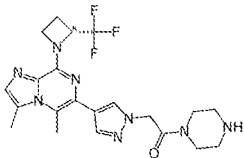
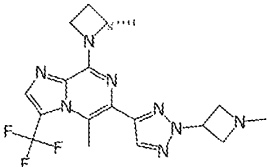
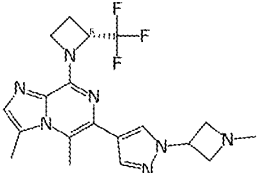
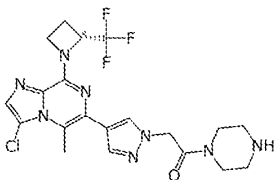
				2H), 2.61 - 2.53 (m, 1H), 2.33 (s, 3H), 2.11 - 1.97 (m, 1H), 1.61 (d, J = 6.2 Hz, 3H)
A52		405.42	m/z 406.2(M+1)+, RT: 2.623 min (Method F)	¹H NMR (400 MHz, CD₃SOCD₃, 299 K) δ (ppm) = 8.07 (s, 1H), 8.01 (s, 1H), 7.80 (s, 1H), 7.65 (s, 1H), 5.33 - 5.13 (m, 1H), 5.03 - 4.89 (m, 1H), 4.50 (dt, J = 5.5, 8.5 Hz, 1H), 4.44 - 4.36 (m, 1H), 2.89 (dd, J = 7.4, 9.4 Hz, 1H), 2.79 - 2.70 (m, 2H), 2.68 - 2.63 (m, 1H), 2.63 - 2.58 (m, 3H), 2.57 - 2.52 (m, 1H), 2.49 - 2.44 (m, 1H), 2.42 - 2.32 (m, 1H), 2.30 (s, 3H), 2.17 - 2.05 (m, 1H)
A53		353.43	m/z 354.2 (M+H)+, RT: 1.584 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 7.83 (d, 1H, J = 0.9 Hz), 7.76 (d, 1H, J = 2.4 Hz), 7.62 (d, 1H, J = 1.1 Hz), 6.74 (d, 1H, J = 2.3 Hz), 5.07 (quin, 1H, J = 7.2 Hz), 4.8-4.8 (m, 1H), 4.48 (quin, 1H, J = 5.8 Hz), 4.2-4.3 (m, 1H), 4.01 (dd, 1H, J = 5.1, 9.3 Hz), 3.9-3.9 (m, 2H), 3.7-3.7 (m, 2H), 2.86 (s, 3H), 2.50 (s, 3H), 1.60 (d, 3H, J = 6.4 Hz)
A54		337.43	m/z 338.3 (M+H)+, RT: 1.653 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 7.81 (s, 1H), 7.76 (d, J=2.38 Hz, 1H), 7.60 (s, 1H), 6.72 (d, J=2.25 Hz, 1H), 5.07 (quin, J=7.13 Hz, 1H), 4.78 - 4.85 (m, 1H),

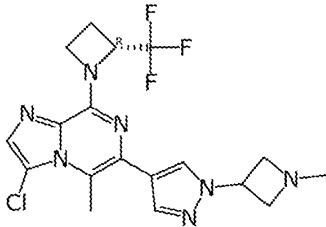
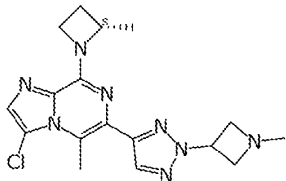
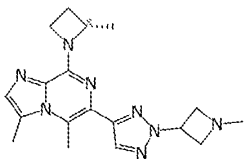
				4.54 (td, $J=8.88$, 5.25 Hz, 1 H), 4.25 - 4.33 (m, 1 H), 3.89 - 3.95 (m, 2 H), 3.70 (t, $J=7.75$ Hz, 2 H), 2.82 (s, 3 H), 2.53 - 2.60 (m, 1 H), 2.51 (s, 3 H), 2.05 - 2.13 (m, 1 H), 1.60 (d, $J=6.13$ Hz, 3 H)
A55		341.39	m/z 342.2 (M+H, M+2) ⁺ , RT: 1.745 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.96 (s, 1 H), 7.76 (d, $J = 2.38$ Hz, 1 H), 7.16 (d, $J = 7.13$ Hz, 1 H), 6.75 (d, $J = 2.38$ Hz, 1 H), 5.04 (quin, $J = 7.07$ Hz, 1 H), 4.89 - 4.94 (m, 1 H), 4.55 (td, $J = 9.16$, 5.57 Hz, 1 H), 4.39 (td, $J = 9.22$, 6.82 Hz, 1 H), 3.84 - 3.89 (m, 2 H), 3.65 - 3.70 (m, 2 H), 2.56 - 2.66 (m, 1 H), 2.50 (s, 3 H), 2.10 (ddt, $J = 10.90$, 9.05, 6.35, 6.35 Hz, 1 H), 1.65 (d, $J = 6.13$ Hz, 3 H)
A56		357.39	358.2 (M+H) ⁺ , RT: 1.733 min (Method P)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.04 (s, 1 H), 7.90 (d, $J = 2.38$ Hz, 1 H), 7.33 (d, $J = 7.13$ Hz, 1 H), 6.75 (d, $J = 2.25$ Hz, 1 H), 5.41 (quin, $J = 6.63$ Hz, 1 H), 4.42 - 4.71 (m, 6 H), 4.16 - 4.21 (m, 1 H), 4.02 - 4.11 (m, 2 H), 3.06 (br s, 3 H), 1.62 (d, $J = 6.38$ Hz, 3 H)

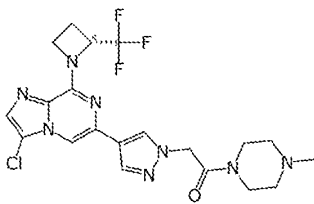
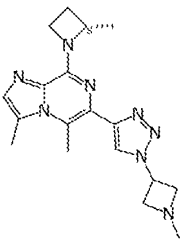
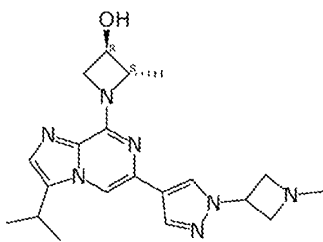
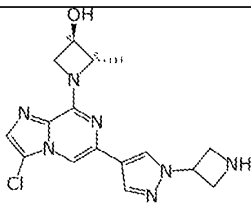
A57		338.42	m/z 339.2 (M+H) ⁺ , RT: 1.517 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> 4) δ 8.09 (s, 1 H), 7.84 (d, <i>J</i> = 0.75 Hz, 1 H), 7.61 (s, 1 H), 5.36 (quin, <i>J</i> = 6.97 Hz, 1 H), 4.80 - 4.86 (m, 1 H), 4.55 (td, <i>J</i> = 8.94, 5.13 Hz, 1 H), 4.27 - 4.35 (m, 1 H), 3.93 - 3.99 (m, 2 H), 3.76 - 3.83 (m, 2 H), 2.86 (s, 3 H), 2.53 - 2.62 (m, 1 H), 2.51 (s, 3 H), 2.10 (ddt, <i>J</i> = 10.66, 9.07, 6.71, 6.71 Hz, 1 H), 1.61 (d, <i>J</i> = 6.13 Hz, 3 H)
A58		448.35	449.3 (M+H) ⁺ , RT: 2.138 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> 4) δ 8.04 (s, 1 H), 7.99 (s, 1 H), 7.90 - 7.93 (m, 1 H), 7.31 (s, 1 H), 5.20 - 5.29 (m, 1 H), 5.17 (s, 2 H), 4.65 (td, <i>J</i> = 8.57, 5.63 Hz, 1 H), 4.41 (br d, <i>J</i> = 7.00 Hz, 1 H), 3.58 (q, <i>J</i> = 4.42 Hz, 4 H), 2.79 - 2.90 (m, 4 H), 2.55 - 2.72 (m, 2 H), 2.48 (s, 3 H)
A59		394.48	m/z 395.3 (M+H) ⁺ , RT: 3.046 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> 4) δ 8.03 (s, 1 H), 7.95 (s, 1 H), 7.73 (s, 1 H), 7.25 (s, 1 H), 5.17 (s, 2 H), 4.81 - 4.83 (m, 1 H), 4.49 - 4.61 (m, 1 H), 4.27 - 4.38 (m, 1 H), 3.53 - 3.62 (m, 4 H), 2.80 - 2.94 (m, 4 H), 2.51 - 2.62 (m, 1 H), 2.44 (s, 3 H), 2.02 - 2.13 (m, 1 H), 1.61 (d, <i>J</i> = 6.25 Hz, 3 H)

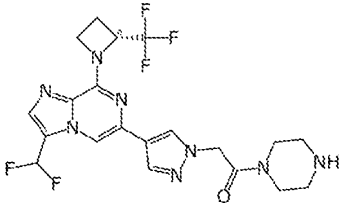
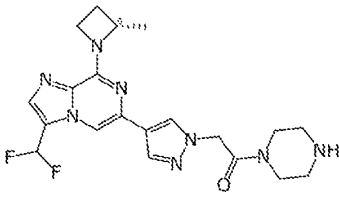
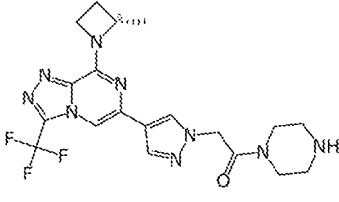
A60		414.90	415.2 (M+H) ⁺ , RT: 1.704 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.08 (s, 1 H), 7.98 (s, 1 H), 7.82 (s, 1 H), 7.46 (s, 1 H), 5.19 (s, 2 H), 4.91 (br s, 1 H), 4.55 (td, <i>J</i> = 9.16, 5.44 Hz, 1 H), 4.34 - 4.43 (m, 1 H), 3.54 - 3.62 (m, 4 H), 2.80 - 2.92 (m, 4 H), 2.56 - 2.67 (m, 1 H), 2.10 (ddt, <i>J</i> = 10.82, 9.10, 6.36, 6.36 Hz, 1 H), 1.65 (d, <i>J</i> = 6.13 Hz, 3 H)
A61		428.93	<i>m/z</i> 429.3 (M+H) ⁺ , RT: 1.638 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.90 (s, 1 H), 7.79 (s, 1 H), 7.42 (s, 1 H), 5.20 (s, 2 H), 4.77 - 4.85 (m, 1 H), 4.49 (td, <i>J</i> = 8.97, 5.44 Hz, 1 H), 4.24 - 4.32 (m, 1 H), 3.58 - 3.63 (m, 4 H), 2.91 (s, 5 H), 2.83 - 2.87 (m, 2 H), 2.50 - 2.60 (m, 1 H), 2.01 - 2.11 (m, 1 H), 1.58 (d, <i>J</i> = 6.25 Hz, 3 H)
A62		387.87	<i>m/z</i> 388.2 (M+H) ⁺ , RT: 1.410 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.00 (s, 1H), 7.83 (s, 1H), 7.44 (s, 1H), 5.08 (quin, 1H, <i>J</i> = 7.2 Hz), 4.73 (dd, 1H, <i>J</i> = 6.7, 9.6 Hz), 4.4-4.5 (m, 1H), 4.2-4.3 (m, 1H), 4.00 (dd, 1H, <i>J</i> = 4.9, 9.6 Hz), 3.88 (t, 2H, <i>J</i> = 8.0 Hz), 3.66 (t, 2H, <i>J</i> = 7.7 Hz), 2.90 (s, 3H), 2.49 (s, 3H), 1.58 (d, 3H, <i>J</i> = 6.4 Hz)

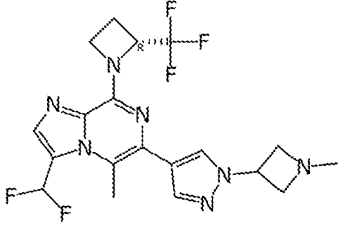
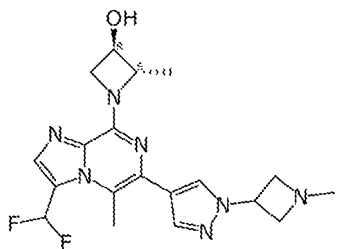
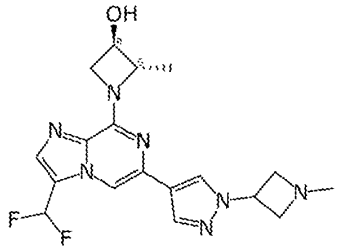
A63		351.46	m/z 352.2 (M+H) ⁺ , RT: 1.537 min (Method P)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.09 (s, 1 H), 7.90 (s, 1 H), 7.37 (s, 1 H), 5.39 - 5.60 (m, 1 H), 4.83 - 4.93 (m, 1 H), 4.67 (br s, 2 H), 4.42 - 4.57 (m, 3 H), 4.28 - 4.36 (m, 1 H), 3.04 (s, 3 H), 2.74 (s, 3 H), 2.71 (s, 3 H), 2.55 - 2.60 (m, 1 H), 1.97 - 2.08 (m, 1 H), 1.60 (d, <i>J</i> = 6.13 Hz, 3 H)
A64		367.46	m/z 368.2 (M+H) ⁺ , RT: 1.352 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.99 (s, 1 H), 7.84 (s, 1 H), 7.27 (s, 1 H), 5.10 (quin, <i>J</i> = 7.13 Hz, 1 H), 4.76 (br t, <i>J</i> = 7.82 Hz, 1 H), 4.41 - 4.51 (m, 1 H), 4.22 (q, <i>J</i> = 5.34 Hz, 1 H), 3.94 - 3.99 (m, 1 H), 3.91 (br t, <i>J</i> = 7.88 Hz, 2 H), 3.68 (br t, <i>J</i> = 7.50 Hz, 2 H), 2.84 (s, 3 H), 2.79 (s, 3 H), 2.51 (s, 3 H), 1.58 (br d, <i>J</i> = 6.25 Hz, 3 H)
A65		371.87	m/z 372.2 (M+H) ⁺ , RT: 1.673 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.99 (s, 1 H), 7.81 (s, 1 H), 7.42 (s, 1 H), 5.07 (quin, <i>J</i> = 7.13 Hz, 1 H), 4.78 - 4.83 (m, 1 H), 4.48 (td, <i>J</i> = 9.07, 5.38 Hz, 1 H), 4.28 (td, <i>J</i> = 9.10, 6.94 Hz, 1 H), 3.86 - 3.91 (m, 2 H), 3.63 - 3.69 (m, 2 H), 2.88 (s, 3 H), 2.51 - 2.59 (m, 1 H), 2.49 (s, 3 H), 2.05 (ddt, <i>J</i> = 10.69, 9.07, 6.44, 6.44 Hz, 1 H), 1.58 (d, <i>J</i> = 6.13 Hz, 3 H)

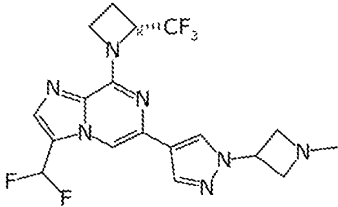
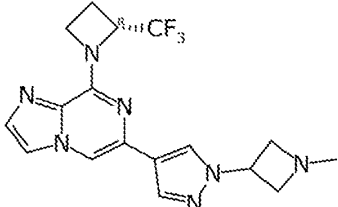
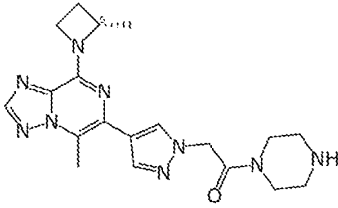
A66		462.48	m/z 463.3 (M+H) ⁺ , RT: 1.581 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.88 (s, 1H), 7.82 (s, 1H), 7.26 (s, 1H), 5.27 - 5.20 (m, 1H), 5.19 (s, 2H), 4.63 - 4.60 (m, 1H), 4.35 - 4.26 (m, 1H), 3.61 - 3.56 (m, 4H), 2.92 - 2.88 (m, 2H), 2.86 (s, 3H), 2.83 (br d, <i>J</i> = 5.0 Hz, 2H), 2.77 (s, 3H), 2.65 - 2.51 (m, 2H)
A67		406.42	m/z 407.3 (M+1) ⁺ , RT: 3.097 min (Method O)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.24 (s, 1 H), 8.13 (s, 1 H), 5.30 (m, 1 H), 4.80 (br d, <i>J</i> = 4.25 Hz, 1 H), 4.45 (br d, <i>J</i> = 4.25 Hz, 1 H), 4.22 - 4.37 (m, 1 H), 3.74 - 3.87 (m, 2 H), 3.46 - 3.60 (m, 2 H), 2.81 (s, 3 H), 2.55 (br s, 1 H), 2.35 (s, 3 H), 2.06 (br d, <i>J</i> = 10.51 Hz, 1 H), 1.58 (d, <i>J</i> = 6.13 Hz, 3 H)
A68		405.43	m/z 406.2 (M+H) ⁺ , RT: 1.944 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.95 (s, 1H), 7.83 (s, 1H), 7.24 (s, 1H), 5.20 (td, <i>J</i> = 6.5, 8.8 Hz, 1H), 5.04 (quin, <i>J</i> = 7.1 Hz, 1H), 4.64 - 4.59 (m, 1H), 4.34 - 4.26 (m, 1H), 3.90 - 3.84 (m, 2H), 3.66 - 3.59 (m, 2H), 2.81 (s, 3H), 2.74 (s, 3H), 2.63 - 2.53 (m, 2H), 2.48 (s, 3H)
A69		482.90	m/z 483.2 (M+H, M+3) ⁺ , RT: 1.999 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.93 (s, 1 H), 7.84 (s, 1 H), 7.48 (s, 1 H), 5.19 - 5.27 (m, 3 H), 4.59 - 4.65 (m, 1 H), 4.36 - 4.45 (m, 1 H), 3.56 - 3.61 (m, 4 H),

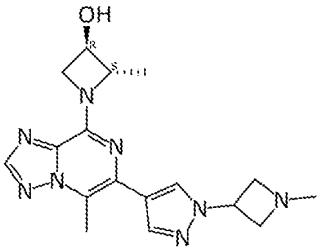
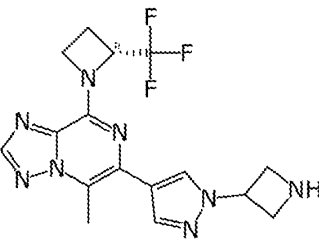
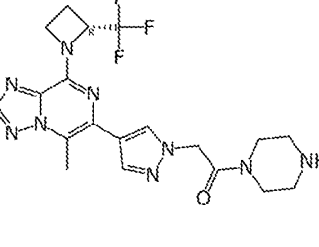
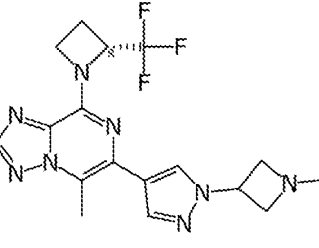
				2.98 (s, 3 H), 2.81 - 2.90 (m, 4 H), 2.52 - 2.70 (m, 2 H)
A70		425.84	m/z 426.2 (M+H) ⁺ , RT: 2.235 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.01 (s, 1 H), 7.87 (s, 1 H), 7.48 (s, 1 H), 5.17 - 5.27 (m, 1 H), 5.07 (quin, <i>J</i> = 7.07 Hz, 1 H), 4.59 - 4.65 (m, 1 H), 4.36 - 4.44 (m, 1 H), 3.88 (br t, <i>J</i> = 7.82 Hz, 2 H), 3.65 (br t, <i>J</i> = 7.63 Hz, 2 H), 2.95 (s, 3 H), 2.54 - 2.68 (m, 2 H), 2.49 (s, 3 H)
A71		372.86	m/z 373.2 (M+H) ⁺ , RT: 1.995 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.02 (s, 1 H), 7.43 (s, 1 H), 5.34 (quin, <i>J</i> = 6.97 Hz, 1 H), 4.77 - 4.83 (m, 1 H), 4.49 (td, <i>J</i> = 9.04, 5.57 Hz, 1 H), 4.25 - 4.34 (m, 1 H), 3.95 (t, <i>J</i> = 8.00 Hz, 2 H), 3.74 - 3.81 (m, 2 H), 3.08 (s, 3 H), 2.52 - 2.59 (m, 1 H), 2.50 (s, 3 H), 2.02 - 2.11 (m, 1 H), 1.59 (d, <i>J</i> = 6.13 Hz, 3 H)
A72		352.45	m/z 353.2 (M+H) ⁺ , RT: 1.698 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.02 (s, 1H), 7.25 (s, 1H), 5.34 (quin, 1H, <i>J</i> = 7.0 Hz), 4.8-4.8 (m, 1H), 4.51 (dt, 1H, <i>J</i> = 5.3, 8.9 Hz), 4.2-4.3 (m, 1H), 3.9-4.0 (m, 2H), 3.7-3.8 (m, 2H), 3.01 (s, 3H), 2.78 (s, 3H), 2.5-2.6 (m, 1H), 2.50 (s, 3H), 2.0-2.1 (m, 1H), 1.57 (d, 3H, <i>J</i> = 6.1 Hz)

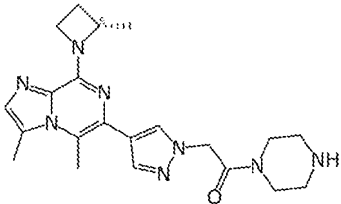
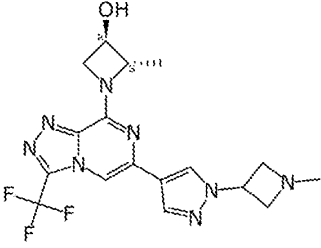
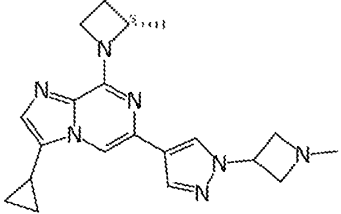
A73		482.90	m/z 483.2 (M+H) ⁺ , RT: 2.627 min (Method O)	¹ H NMR (400 MHz, MeOD-d ₄) δ 8.10 (s, 1 H), 8.02 (s, 2 H), 7.54 (s, 1 H), 5.28 (br d, J = 9.01 Hz, 1 H), 5.21 (s, 2 H), 4.67 (br d, J = 5.50 Hz, 1 H), 4.52 (br d, J = 6.75 Hz, 1 H), 3.65 - 3.70 (m, 4 H), 2.70 (br d, J = 5.50 Hz, 2 H), 2.59 - 2.66 (m, 4 H), 2.43 (s, 3 H)
A74		352.45	m/z 353.2 (M+H) ⁺ , RT: 2.350 min (Method P)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.31 (s, 1H), 7.25 (s, 1H), 5.3-5.4 (m, 1H), 4.8-4.8 (m, 1H), 4.4-4.6 (m, 1H), 4.2-4.3 (m, 1H), 3.94 (br t, 2H, J = 7.7 Hz), 3.7-3.8 (m, 2H), 2.94 (s, 3H), 2.77 (s, 3H), 2.54 (br d, 1H, J = 9.1 Hz), 2.50 (s, 3H), 2.0-2.1 (m, 1H), 1.55 (d, 3H, J = 6.1 Hz)
A75		381.48	m/z 382.3 (M+H) ⁺ , RT: 1.709 min (Method O)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.20 (s, 1H), 8.02 (s, 1H), 7.87 (s, 1H), 7.29 (s, 1H), 5.05 (quin, 1H, J = 7.1 Hz), 4.80 (br d, 1H, J = 8.5 Hz), 4.52 (quin, 1H, J = 5.8 Hz), 4.25 (q, 1H, J = 4.9 Hz), 4.06 (dd, 1H, J = 4.9, 9.4 Hz), 3.88 (t, 2H, J = 7.8 Hz), 3.64 (t, 2H, J = 7.6 Hz), 3.28 (br d, 1H, J = 6.9 Hz), 2.49 (s, 3H), 1.63 (d, 3H, J = 6.4 Hz), 1.40 (dd, 6H, J = 2.1, 6.6 Hz)
A76		359.82	m/z 360.1 (M+H) ⁺ , RT: 1.795 min (Method O)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 1.65 (d, J = 6.38 Hz, 3 H) 3.96 (br t, J = 8.69 Hz, 2 H) 4.07 - 4.17 (m,

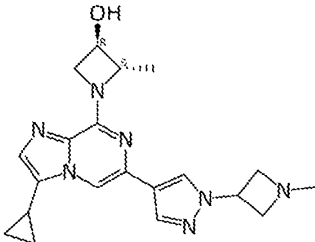
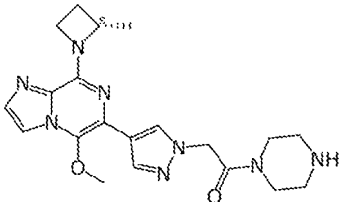
				3 H) 4.23 - 4.29 (m, 1 H) 4.49 - 4.57 (m, 1 H) 4.78 (br dd, $J = 9.07, 7.19$ Hz, 1 H) 5.23 - 5.36 (m, 1 H) 7.46 (s, 1 H) 7.83 (s, 1 H) 8.01 (s, 1 H) 8.20 (s, 1 H)
A77		484.44	485.1 (M+H)+, RT: 2.457 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.13 (s, 1 H) 8.08 (s, 1 H) 7.97 (s, 1 H) 7.79 (s, 1 H) 7.27 (t, $J=53.25$ Hz, 1 H) 5.23 - 5.35 (m, 1 H) 5.19 (s, 2 H) 4.62 - 4.75 (m, 1 H) 4.44 - 4.59 (m, 1 H) 3.57 (br s, 4 H) 2.77 - 2.93 (m, 4 H) 2.65 - 2.76 (m, 1 H) 2.54 - 2.65 (m, 1 H)
A78		430.46	m/z 431.2 (M+H)+, RT: 2.417 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.06 (s, 1 H) 7.94 (d, $J=2.15$ Hz, 2 H) 7.73 (t, $J=1.85$ Hz, 1 H) 7.22 (t, $J=53.23$ Hz, 1 H) 5.18 (s, 2 H) 4.88 - 4.93 (m, 1 H) 4.56 (td, $J=9.12, 5.48$ Hz, 1 H) 4.34 - 4.44 (m, 1 H) 3.58 (br t, $J=4.71$ Hz, 4 H) 2.76 - 2.92 (m, 4 H) 2.54 - 2.67 (m, 1 H) 2.10 (ddt, $J=10.85, 9.03, 6.39$ Hz, 1 H) 1.65 (d, $J=6.32$ Hz, 3 H)
A79		337.43	m/z 338.2 (M+H)+, RT: 2.431min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.14 (s, 1 H) 8.04 (s, 1 H) 7.88 (s, 1 H) 5.25 (s, 2 H) 4.94 - 5.04 (m, 1 H) 4.40 - 4.79 (m, 2 H) 3.87 (br s, 4 H) 3.34 (br d, $J=4.28$ Hz, 2 H) 3.26 (br s, 2 H) 2.65 -

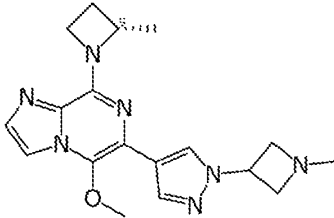
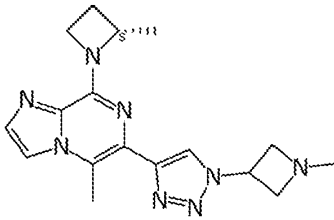
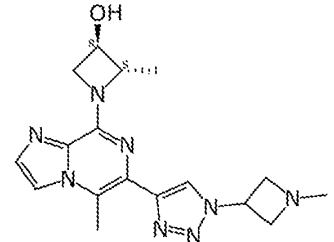
				2.79 (m, 1 H) 2.13 - 2.25 (m, 1 H) 1.71 (d, $J=6.11$ Hz, 3 H)
A80		441.41	m/z 442.2 (M+H) ⁺ , RT: 2.093 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.06 (s, 1 H), 7.91 (br s, 2 H), 7.47 (t, $J = 54.22$ Hz, 1 H), 5.22 - 5.32 (m, 1 H), 5.08 (t, $J = 7.07$ Hz, 1 H), 4.67 (br d, $J = 5.63$ Hz, 1 H), 4.43 (br d, $J = 7.88$ Hz, 1 H), 3.89 (t, $J = 7.63$ Hz, 2 H), 3.66 (t, $J = 7.38$ Hz, 2 H), 2.79 (s, 3 H), 2.55 - 2.70 (m, 2 H), 2.49 (s, 3 H)
A81		403.44	m/z 404.2 (M+H) ⁺ , RT: 1.212 min (Method O)	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 8.05 (s, 1 H) 7.87 (s, 2 H) 7.45 (t, $J = 53.32$ Hz, 1 H) 5.09 (t, $J = 7.13$ Hz, 1 H) 4.69 - 4.83 (m, 1 H) 4.41 - 4.55 (m, 1 H) 4.23 (br d, $J = 6.00$ Hz, 1 H) 4.05 (s, 1 H) 3.86 - 3.95 (m, 2 H) 3.63 - 3.76 (m, 2 H) 2.75 (s, 3 H) 2.50 (s, 3 H) 1.60 (d, $J = 6.38$ Hz, 3 H)
A82		389.41	m/z 390.2 (M+H) ⁺ , RT: 1.505 min (Method O)	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 8.21 (s, 1 H) 8.00 (d, $J = 4.88$ Hz, 2 H) 7.75 (s, 1 H) 7.24 (t, $J = 53.45$ Hz, 1 H) 5.07 (s, 1 H) 4.81 (br d, $J = 2.13$ Hz, 1 H) 4.55 (br s, 1 H) 4.22 - 4.33 (m, 1 H) 4.12 (dd, $J = 9.94, 4.82$ Hz, 1 H) 3.83 - 3.93 (m, 2 H) 3.66 (dd, $J = 8.57, 7.07$ Hz, 2 H) 2.49 (s, 3 H) 1.66 (d, $J = 6.50$ Hz, 3 H)

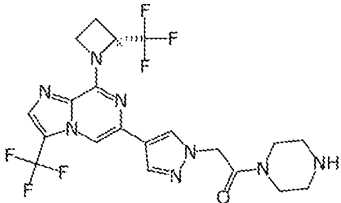
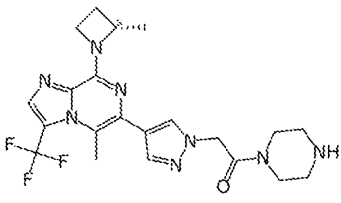
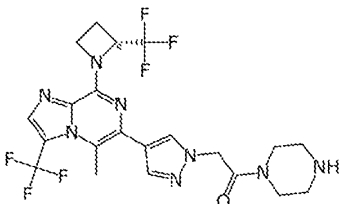
A83		427.38	m/z 428.3 (M+H) ⁺ , RT: 1.799 min (Method P)	¹ H NMR (400 MHz, MeOD) δ (ppm) = 8.24 (s, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.45 - 7.12 (m, 1H), 5.37 - 5.25 (m, 1H), 5.07 (quin, J = 7.1 Hz, 1H), 4.71 (dt, J = 5.8, 8.7 Hz, 1H), 4.60 - 4.49 (m, 1H), 3.93 - 3.86 (m, 2H), 3.69 - 3.60 (m, 2H), 2.79 - 2.69 (m, 1H), 2.68 - 2.58 (m, 1H), 2.50 (s, 3H)
A84		377.38	378.3 (M+H) ⁺ , RT: 2.040 min (Method O)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.98 (s, 1H), 7.82 (d, 1H, J = 1.0 Hz), 7.56 (d, 1H, J = 1.0 Hz), 5.2-5.4 (m, 1H), 5.0-5.1 (m, 1H), 4.69 (dt, 1H, J = 5.6, 8.6 Hz), 4.4- 4.5 (m, 1H), 3.8-3.9 (m, 2H), 3.5-3.7 (m, 2H), 2.5-2.8 (m, 2H), 2.48 (s, 3H)
A85		395.47	m/z 396.2 (M+H) ⁺ , RT: 2.237 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.30 (s, 1 H) 8.00 (s, 1 H) 7.89 (s, 1 H) 5.20 (s, 2 H) 4.74 - 4.83 (m, 1 H) 4.44 (td, J=8.94, 5.25 Hz, 1 H) 4.23 - 4.32 (m, 1 H) 3.50 - 3.66 (m, 4 H) 2.86 - 2.91 (m, 2 H) 2.80 - 2.84 (m, 2 H) 2.72 (s, 3 H) 2.50 - 2.62 (m, 1 H) 2.10 (ddt, J=10.76, 9.07, 6.60, 6.60 Hz, 1 H) 1.62 (d, J=6.25 Hz, 3 H)

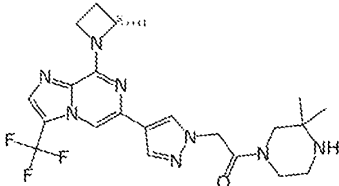
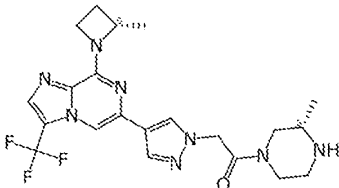
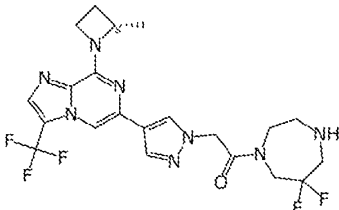
A86		354.41	m/z 355.1 (M+H) ⁺ , RT: 2.126 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 1.64 (d, J=6.44 Hz, 3 H) 2.49 (s, 3 H) 2.78 (s, 3 H) 3.67 (t, J=7.69 Hz, 2 H) 3.84 – 3.94 (m, 2 H) 4.03 (dd, J=9.54, 5.01 Hz, 1 H) 4.23 – 4.31 (m, 1 H) 4.43 – 4.53 (m, 1 H) 4.66 – 4.77 (m, 1 H) 5.10 (t, J=7.09 Hz, 1 H) 7.97 (s, 1 H) 8.13 (s, 1 H) 8.35 (s, 1 H)
A87		378.36	m/z 379.1 (M+H) ⁺ , RT: 2.399 min (Method J)	¹ H NMR (400 MHz, METHANOL-d ₄) δ = 8.41 (s, 1H), 8.14 (s, 1H), 8.11 (s, 1H), 5.52 (quin, J = 7.3 Hz, 1H), 5.24 (td, J = 6.4, 8.9 Hz, 1H), 4.68 – 4.55 (m, 5H), 4.51 – 4.41 (m, 1H), 2.83 (s, 3H), 2.77 – 2.57 (m, 2H)
A88		449.44	m/z 450.3 (M+H) ⁺ , RT: 1.757 min (Method P)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.40 (s, 1 H), 8.07 (s, 1 H), 7.98 (s, 1 H), 5.24 - 5.30 (m, 1 H), 5.23 (s, 2 H), 4.63 (td, J=8.60, 5.57 Hz, 1 H), 4.42 - 4.50 (m, 1 H), 3.56 - 3.63 (m, 4 H), 2.87 - 2.91 (m, 2 H), 2.84 (s, 3 H), 2.82 (br s, 2 H), 2.58 - 2.76 (m, 2 H)
A89		392.39	m/z 393.2 (M+H) ⁺ , RT: 1.910 min (Method P)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.39 (s, 1 H), 8.14 (s, 1 H), 8.00 (s, 1 H), 5.20 - 5.30 (m, 1 H), 5.09 (quin, J = 7.10 Hz, 1 H), 4.62 (td, J = 8.57, 5.63 Hz, 1 H), 4.41 - 4.49 (m, 1 H), 3.86 -

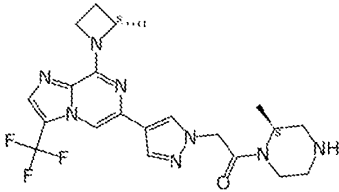
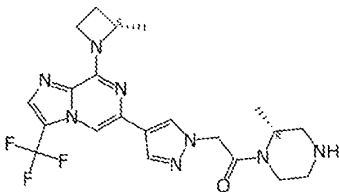
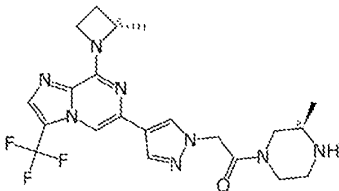
				3.91 (m, 2 H), 3.64 - 3.69 (m, 2 H), 2.81 (s, 3 H), 2.67 - 2.75 (m, 1 H), 2.58 - 2.66 (m, 1 H), 2.49 (s, 3 H)
A90		408.51	m/z 409.3 (M+H) ⁺ , RT: 1.393 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 7.86 (s, 1H), 7.77 (s, 1H), 7.21 (s, 1H), 5.19 (s, 2H), 4.7-4.8 (m, 1H), 4.49 (dt, 1H, <i>J</i> = 5.3, 8.8 Hz), 4.2-4.3 (m, 1H), 3.5-3.6 (m, 4H), 2.9-2.9 (m, 2H), 2.8-2.9 (m, 2H), 2.79 (s, 3H), 2.74 (s, 3H), 2.5-2.6 (m, 1H), 2.0-2.1 (m, 1H), 1.55 (d, 3H, <i>J</i> = 6.1 Hz)
A91		408.39	m/z 409.2 (M+H) ⁺ , RT: 2.369 min (Method F)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 - 10.24 (m, 1 H) 8.41 (s, 1 H) 8.32 (s, 1 H) 8.08 (s, 1 H) 5.86 (br d, <i>J</i> =5.75 Hz, 1 H) 5.34 - 5.53 (m, 1 H) 4.69 - 4.89 (m, 1 H) 4.58 (br d, <i>J</i> =1.71 Hz, 2 H) 4.46 - 4.53 (m, 1 H) 4.33 - 4.44 (m, 2 H) 4.21 - 4.27 (m, 1 H) 4.03 - 4.19 (m, 1 H) 2.97 (s, 3 H) 1.63 (br d, <i>J</i> =6.24 Hz, 3 H)
A92		363.46	m/z 364.2 (M+1) ⁺ , RT: 2.668 min (Method F)	¹ H NMR (400 MHz, CD ₃ OD, 298 K) δ (ppm) = 8.17 (s, 1H), 8.06 - 7.87 (m, 2H), 7.16 (s, 1H), 5.04 (quin, <i>J</i> = 7.0 Hz, 1H), 4.84 - 4.79 (m, 1H), 4.62 - 4.47 (m, 1H), 4.38 - 4.25 (m, 1H), 3.86 (br t, <i>J</i> = 7.7 Hz, 2H), 3.63 (br t, <i>J</i> = 7.5 Hz,

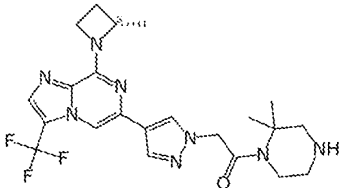
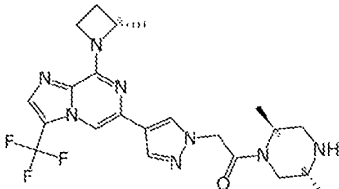
				2H), 2.66 - 2.51 (m, 1H), 2.48 (s, 3H), 2.13 - 2.00 (m, 1H), 1.98 - 1.89 (m, 1H), 1.61 (br d, J = 6.1 Hz, 3H), 1.08 (br d, J = 6.7 Hz, 2H), 0.72 (br d, J = 3.8 Hz, 2H)
A93		379.5	m/z 380.2 (M+H) ⁺ , RT: 1.592 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.22 (d, J=5.48 Hz, 2 H) 8.13 (s, 1 H) 7.46 (s, 1 H) 5.46 (br t, J=6.97 Hz, 1 H) 4.89 - 4.95 (m, 2 H) 4.48 - 4.79 (m, 4 H) 4.32 (dt, J=6.44, 4.47 Hz, 1 H) 4.13 (dd, J=9.54, 4.65 Hz, 1 H) 2.95 - 3.26 (m, 3 H) 1.96 - 2.07 (m, 1 H) 1.65 (d, J=6.44 Hz, 3 H) 1.05 - 1.29 (m, 2 H) 0.82 (q, J=5.13 Hz, 2 H)
A94		410.47	m/z 411.2 (M+H) ⁺ , RT: 1.514 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 1.69 (d, J=6.20 Hz, 3 H) 2.12 - 2.24 (m, 1 H) 2.64 - 2.79 (m, 1 H) 3.23 - 3.30 (m, 2 H) 3.34 - 3.40 (m, 2 H) 3.84 - 3.92 (m, 4 H) 3.92 - 3.95 (m, 3 H) 4.42 (td, J=9.39, 6.50 Hz, 1 H) 4.66 (td, J=9.12, 6.08 Hz, 1 H) 5.03 - 5.15 (m, 1 H) 5.32 (s, 2 H) 7.76 (d, J=1.31 Hz, 1 H) 7.99 (s, 1 H) 8.03 (d, J=1.31 Hz, 1 H) 8.14 (s, 1 H)

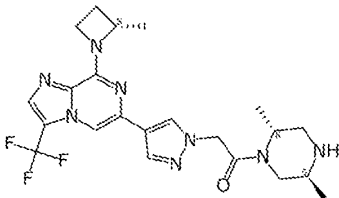
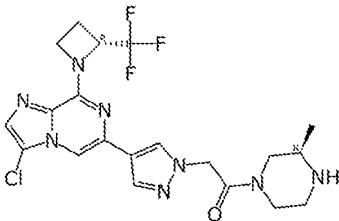
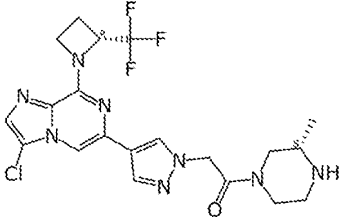
A95		353.42	m/z 354.2 (M+1)⁺, RT: 1.712 min (Method I)	¹H NMR (400 MHz, CD₃OD, 298 K) δ 8.18 (d, J = 1.8 Hz, 2H), 7.96 (d, J = 1.3 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 5.58 - 5.37 (m, 1H), 5.00 - 4.91 (m, 2H), 4.76 - 4.67 (m, 1H), 4.65 - 4.56 (m, 2H), 4.55 - 4.48 (m, 1H), 4.35 (dt, J = 6.8, 9.1 Hz, 1H), 3.94 (s, 3H), 3.27 - 3.04 (m, 3H), 2.72 - 2.54 (m, 1H), 2.15 (tdd, J = 6.5, 9.1, 10.9 Hz, 1H), 1.65 (d, J = 6.2 Hz, 3H)
A96		338.42	m/z 339.2 (M+H)⁺, RT: 1.742 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.52 (s, 1 H), 8.09 (s, 1 H), 7.85 (d, J = 0.63 Hz, 1 H), 5.77 (br t, J = 6.94 Hz, 1 H), 5.18 - 5.33 (m, 1 H), 4.98 (br s, 1 H), 4.59 - 4.85 (m, 4 H), 4.53 (td, J = 9.82, 6.13 Hz, 1 H), 3.17 (br s, 3 H), 2.75 - 2.91 (m, 1 H), 2.67 (s, 3 H), 2.14 - 2.27 (m, 1 H), 1.74 (d, J = 6.38 Hz, 3 H)
A97		354.42	m/z 355.2 (M+H)⁺, RT: 1.307 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.37 (s, 1H), 7.84 (d, 1H, J = 0.9 Hz), 7.62 (d, 1H, J = 1.0 Hz), 5.36 (t, 1H, J = 6.8 Hz), 4.7-4.8 (m, 1H), 4.49 (quin, 1H, J = 5.8 Hz), 4.24 (td, 1H, J = 4.8, 6.4 Hz), 4.02 (dd, 1H, J = 5.0, 9.4 Hz), 3.9-4.0 (m, 2H), 3.7-3.8 (m, 2H), 2.84 (s, 3H), 2.50 (s, 3H), 1.60 (d, 3H, J = 6.4 Hz)

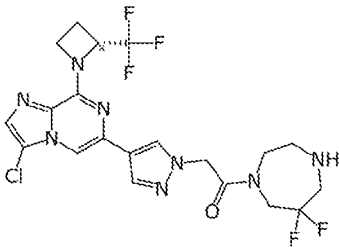
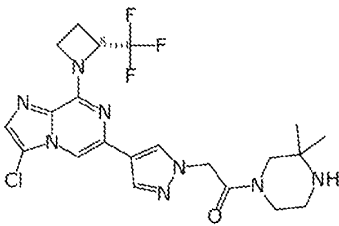
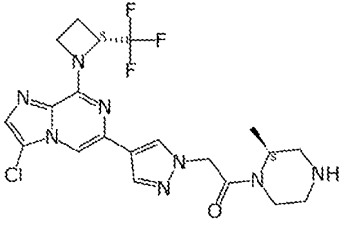
A98		502.43	m/z 503.2 (M+H)⁺, RT: 2.109 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.11 - 8.14 (m, 1 H), 8.03 - 8.05 (m, 1 H), 8.00 - 8.02 (m, 1 H), 7.94 - 7.97 (m, 1 H), 5.26 - 5.34 (m, 1 H), 5.20 (s, 2 H), 4.67 - 4.73 (m, 1 H), 4.54 - 4.60 (m, 1 H), 3.53 - 3.64 (m, 4 H), 2.78 - 3.00 (m, 4 H), 2.73 (ddd, <i>J</i>=12.29, 5.78, 3.06 Hz, 1 H), 2.57 - 2.65 (m, 1 H)
A99		462.48	m/z 463.3 (M+H)⁺, RT: 1.904 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.00 (s, 1 H), 7.96 (s, 1 H), 7.84 (s, 1 H), 5.22 (s, 2 H), 4.89 - 4.94 (m, 1 H), 4.49 - 4.57 (m, 1 H), 4.30 - 4.38 (m, 1 H), 3.60 (br s, 4 H), 2.90 (br s, 2 H), 2.84 (br s, 2 H), 2.72 (br s, 3 H), 2.55 - 2.62 (m, 1 H), 2.05 - 2.14 (m, 1 H), 1.61 (br d, <i>J</i> = 6.13 Hz, 3 H)
A100		516.45	m/z 517.3 (M+H)⁺, RT: 2.151min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.06 (s, 1H), 7.99 (s, 1H), 7.89 (s, 1H), 5.30 - 5.24 (m, 1H), 5.22 (s, 2H), 4.68 (dt, <i>J</i> = 5.7, 8.7 Hz, 1H), 4.51 - 4.43 (m, 1H), 3.62 - 3.57 (m, 4H), 2.92 - 2.87 (m, 2H), 2.86 - 2.81 (m, 2H), 2.78 (d, <i>J</i> = 1.4 Hz, 3H), 2.71 - 2.56 (m, 2H)

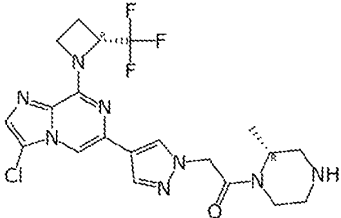
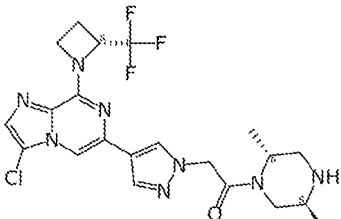
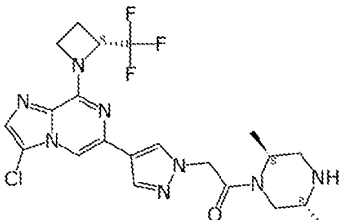
A101		476.51	m/z 477.2 (M+H) ⁺ , RT: 2.053 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.11 (s, 1 H) 7.96 (d, J=2.93 Hz, 1 H) 7.88 (s, 1 H) 7.83 (s, 1 H) 5.11 - 5.28 (m, 2 H) 4.93 (br s, 1 H) 4.51 - 4.61 (m, 1 H) 4.34 - 4.48 (m, 1 H) 3.48 - 3.62 (m, 2 H) 3.36 (br d, J=2.08 Hz, 2 H) 3.24 (s, 1 H) 2.89 (dt, J=17.51, 5.18 Hz, 2 H) 2.54 - 2.70 (m, 1 H) 2.11 (ddt, J=10.91, 9.05, 6.28, 6.28 Hz, 1 H) 1.94 (s, 1 H) 1.66 (d, J=6.24 Hz, 3 H) 1.20 (s, 3 H) 1.11 (s, 3 H)
A102		462.48	m/z 463.2 (M+H) ⁺ , RT: 2.720 min (Method F)	¹ H NMR (400 MHz, DMSO-d ₆) δ 0.99 (d, J=5.96 Hz, 3 H) 1.64 (d, J=6.20 Hz, 3 H) 2.06 (ddt, J=10.76, 8.97, 6.29, 6.29 Hz, 1 H) 2.19 - 2.46 (m, 1 H) 2.53 - 2.73 (m, 4 H) 2.86 - 2.92 (m, 1 H) 3.65 - 4.26 (m, 2 H) 4.31 - 4.57 (m, 2 H) 4.79 - 4.94 (m, 1 H) 5.11 (br s, 2 H) 7.86 (s, 1 H) 7.93 (s, 1 H) 8.01 (d, J=0.95 Hz, 1 H) 8.14 (s, 1 H)
A103		498.46	m/z 499.2 (M+H) ⁺ , RT: 2.883 min (Method F)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.10 (d, J=5.26 Hz, 1 H) 7.96 (d, J=2.08 Hz, 1 H) 7.87 (s, 1 H) 7.82 (s, 1 H) 5.24 (d, J=9.17 Hz, 2 H) 4.88 - 4.94 (m, 1 H) 4.50 - 4.65 (m, 1 H) 4.42 (br d, J=7.21 Hz, 1 H) 3.97 - 4.19 (m, 2 H) 3.70 (br t, J=5.32 Hz,

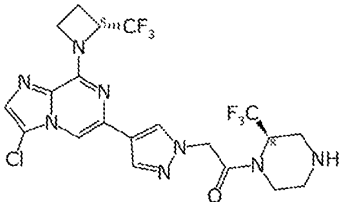
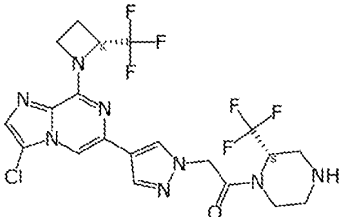
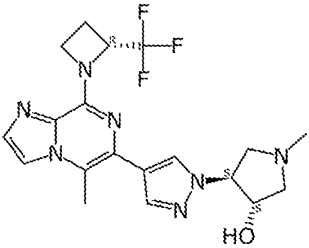
				2 H) 3.09 - 3.27 (m, 2 H) 3.04 (br t, J=5.32 Hz, 1 H) 2.96 (br t, J=5.32 Hz, 1 H) 2.56 - 2.68 (m, 1 H) 2.04 - 2.17 (m, 1 H) 1.66 (d, J=6.11 Hz, 3 H)
A104		462.5	m/z 463.2 (M+H) ⁺ , RT: 2.087 min (Method E)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.10 (br s, 1 H) 7.96 (s, 1 H) 7.88 (s, 1 H) 7.83 (s, 1 H) 4.99 - 5.38 (m, 2 H) 4.89 - 4.95 (m, 1 H) 4.53 - 4.62 (m, 2 H) 4.37 - 4.48 (m, 1 H) 4.06 - 4.29 (m, 1 H) 3.34 - 3.78 (m, 1 H) 2.53 - 3.07 (m, 5 H) 2.05 - 2.18 (m, 1 H) 1.66 (d, J=6.11 Hz, 3 H) 1.18 - 1.52 (m, 3 H)
A105		462.48	m/z 463.2 (M+1) ⁺ , RT: 2.712min (Method F)	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.14 (br d, J=6.20 Hz, 1 H) 8.00 (s, 1 H) 7.92 (s, 1 H) 7.85 (s, 1 H) 5.08 - 5.31 (m, 1 H) 4.87 - 5.08 (m, 2 H), 4.32 - 4.54 (m, 3 H) 3.81 (br d, J=10.13 Hz, 1 H) 2.90 - 3.42 (m, 1 H) 2.52 - 2.89 (m, 5 H) 1.96 - 2.11 (m, 1 H) 1.60 (d, J=6.20 Hz, 3 H) 1.08 - 1.32 (m, 3 H)
A106		462.48	m/z 463.2 (M+H) ⁺ , RT: 2.721 min (Method F)	¹ H NMR (400 MHz, DMSO-d ₆) δ 0.99 (d, J=5.96 Hz, 3 H) 1.64 (d, J=6.20 Hz, 3 H) 2.06 (ddt, J=10.80, 8.90, 6.30, 6.30 Hz, 1 H) 2.14 - 2.45 (m, 1 H) 2.54 - 2.75 (m, 4 H) 2.86 - 2.92 (m, 1 H) 3.62 - 4.23 (m, 2 H) 4.32 - 4.55 (m, 2 H) 4.79 - 4.94 (m, 1 H) 5.11 (br s, 2 H)

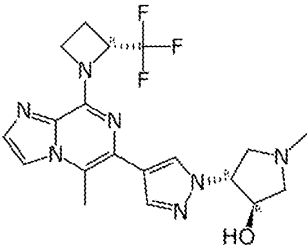
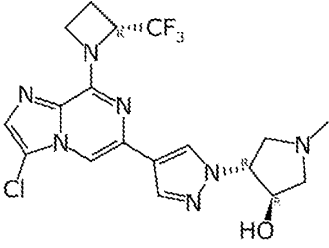
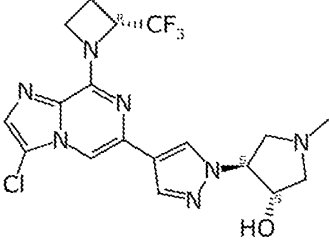
				7.86 (s, 1 H) 7.93 (s, 1 H) 8.01 (d, J=0.95 Hz, 1 H) 8.14 (s, 1 H)
A107		476.51	m/z 477.2 (M+H) ⁺ , RT: 2.131 min (MethoE)	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.06 (s, 1 H) 7.96 (s, 1 H) 7.88 (s, 1 H) 7.84 (s, 1 H) 5.11 (s, 2 H) 4.91 - 4.95 (m, 1 H) 4.58 (br s, 1 H) 4.37 - 4.48 (m, 1 H) 3.43 - 3.57 (m, 2 H) 2.93 - 3.01 (m, 2 H) 2.70 (s, 2 H) 2.57 - 2.67 (m, 1 H) 2.05 - 2.18 (m, 1 H) 1.67 (d, J=6.24 Hz, 3 H) 1.45 (s, 6 H)
A108		476.51	m/z 477.2 (M+H) ⁺ , RT: 0.558 min (Method C)	¹ H NMR (400 MHz, DMSO- d ₆) δ 8.16 (s, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.86 (s, 1H), 5.19 - 4.98 (m, 2H), 4.92 - 4.81 (m, 1H), 4.49 (dt, J = 5.8, 9.2 Hz, 1H), 4.43 - 4.33 (m, 1H), 4.17 (br s, 1H), 3.61 (br d, J = 13.1 Hz, 1H), 3.30 - 3.19 (m, 1H), 3.11 (br d, J = 5.0 Hz, 2H), 2.68 - 2.53 (m, 1H), 2.44 (dd, J = 2.4, 13.1 Hz, 1H), 2.12 - 1.97 (m, 1H), 1.65 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H)

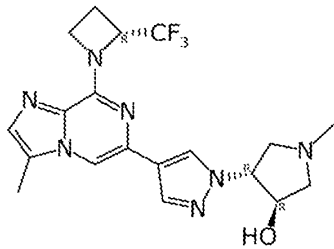
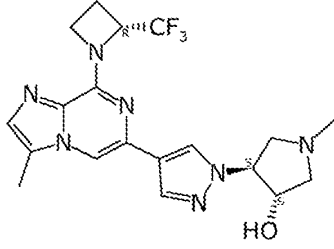
A109		476.51	m/z 477.1 (M+H) ⁺ , RT: 0.389 min (Method D)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.16 (s, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.86 (s, 1H), 5.17 - 4.98 (m, 2H), 4.91 - 4.82 (m, 1H), 4.49 (dt, <i>J</i> = 5.9, 9.1 Hz, 1H), 4.43 - 4.34 (m, 1H), 4.17 (br s, 1H), 3.61 (br d, <i>J</i> = 13.1 Hz, 1H), 3.23 (br dd, <i>J</i> = 3.0, 13.1 Hz, 1H), 3.12 - 3.07 (m, 2H), 2.66 - 2.54 (m, 1H), 2.44 (dd, <i>J</i> = 2.4, 13.1 Hz, 1H), 2.06 (tdd, <i>J</i> = 6.2, 9.0, 10.8 Hz, 1H), 1.65 (d, <i>J</i> = 6.2 Hz, 3H), 1.23 (d, <i>J</i> = 6.8 Hz, 3H), 1.08 (d, <i>J</i> = 6.8 Hz, 3H)
A110		482.90	m/z 483.2 (M+H) ⁺ , RT: 1.971 min (Method P)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.11 (s, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.65 (s, 1 H), 5.26 - 5.37 (m, 1 H), 5.12 (br s, 2 H), 4.49 - 4.61 (m, 2 H), 3.68 - 4.22 (m, 2 H), 2.89 (br d, <i>J</i> = 11.88 Hz, 1 H), 2.57 - 2.79 (m, 4 H), 2.52 - 2.56 (m, 1 H), 2.10 - 2.32 (m, 1 H), 0.99 (br d, <i>J</i> = 5.75 Hz, 3 H)
A111		482.90	m/z 483.3 (M+H) ⁺ , RT: 1.954 min (Method P)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.11 (s, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.65 (s, 1 H), 5.32 (dt, <i>J</i> = 8.97, 6.39 Hz, 1 H), 5.12 (br s, 2 H), 4.47 - 4.61 (m, 2 H), 3.61 - 4.29 (m, 2 H), 2.89 (br d, <i>J</i> = 11.76 Hz, 2 H), 2.68 - 2.81 (m, 2 H), 2.60 (br d, <i>J</i> = 1.25 Hz, 2 H),

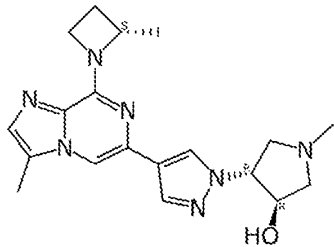
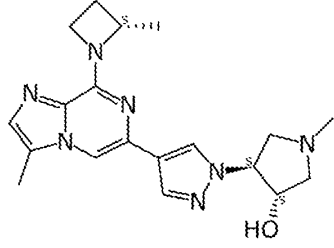
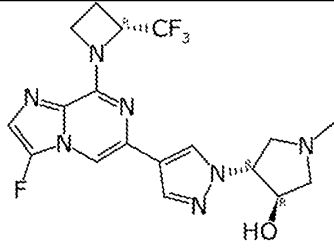
				2.08 - 2.28 (m, 1 H), 0.99 (br d, $J = 5.75$ Hz, 3 H)
A112		518.88	m/z 519.2 (M+H) ⁺ , RT: 2.811 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.11 (d, $J = 5.5$ Hz, 1H), 8.02 (s, 2H), 7.54 (s, 1H), 5.34 - 5.27 (m, 1H), 5.26 (d, $J = 7.9$ Hz, 2H), 4.67 (br dd, $J = 3.2, 8.8$ Hz, 1H), 4.55 - 4.49 (m, 1H), 4.18 - 4.00 (m, 2H), 3.75 - 3.65 (m, 2H), 3.23 - 3.11 (m, 2H), 3.05 (br t, $J = 5.4$ Hz, 1H), 2.97 (t, $J = 5.5$ Hz, 1H), 2.77 - 2.67 (m, 1H), 2.64 - 2.54 (m, 1H)
A113		496.92	m/z 497.2 (M+H) ⁺ , RT: 2.724 min (Method P)	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.11 (s, 1H), 8.03 - 7.99 (m, 2H), 7.53 (s, 1H), 5.28 (td, $J = 6.4, 8.9$ Hz, 1H), 5.23 (s, 2H), 5.15 (s, 1H), 4.70 - 4.63 (m, 1H), 4.55 - 4.47 (m, 1H), 3.57 (br s, 1H), 3.39 (br s, 2H), 2.98 - 2.94 (m, 1H), 2.93 - 2.88 (m, 1H), 2.75 - 2.67 (m, 1H), 2.61 (qd, $J = 6.1, 8.5$ Hz, 1H), 1.25 - 1.18 (m, 3H), 1.14 (s, 3H)
A114		482.90	m/z 483.2 (M+H) ⁺ , RT: 1.963 min (Method P)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.11 (s, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.65 (s, 1 H), 5.27 - 5.36 (m, 1 H), 5.10 (br s, 2 H), 4.49 - 4.61 (m, 2 H), 4.13 - 4.37 (m, 1 H), 3.68 - 3.96 (m, 1 H), 2.89 (br d, $J = 12.63$ Hz, 1 H), 2.69 - 2.78 (m, 3 H), 2.51 - 2.58 (m, 2 H),

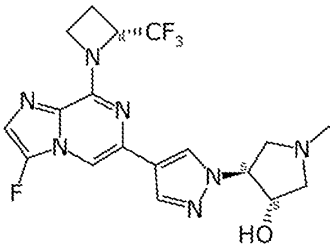
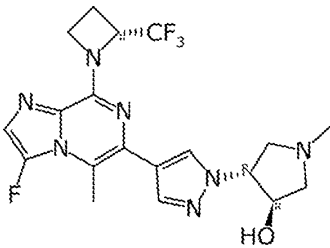
				2.11 - 2.33 (m, 1 H), 1.24 (br d, $J = 6.50$ Hz, 3 H)
A115		482.90	m/z 483.3 ($M+H$)⁺, RT: 1.941 min (Method P)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.11 (s, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.65 (s, 1 H), 5.27 - 5.39 (m, 1 H), 5.09 (br s, 2 H), 4.50 - 4.62 (m, 2 H), 4.18 - 4.35 (m, 1 H), 3.69 - 3.92 (m, 1 H), 2.89 (br d, $J = 12.63$ Hz, 1 H), 2.68 - 2.82 (m, 3 H), 2.51 - 2.58 (m, 2 H), 2.19 (br s, 1 H), 1.23 (br d, $J = 6.25$ Hz, 3 H)
A116		496.92	m/z 497.3 ($M+H$)⁺, RT: 2.743 min (Method P)	¹ H NMR (400 MHz, CHLOROFORM- d) δ 7.99 (s, 1 H), 7.93 (s, 1 H), 7.69 (s, 1 H), 7.47 (s, 1 H), 5.19 - 5.26 (m, 1 H), 5.02 (br s, 2 H), 4.73 - 4.78 (m, 1 H), 4.57 (br d, $J = 7.25$ Hz, 1 H), 4.23 - 4.54 (m, 1 H), 3.17 - 3.48 (m, 4 H), 2.64 - 2.71 (m, 2 H), 2.56 - 2.60 (m, 1 H), 1.31 (br d, $J = 6.75$ Hz, 3 H), 1.17 (d, $J = 6.75$ Hz, 3 H)
A117		496.92	m/z 497.3 ($M+H$)⁺, RT: 2.702 min (Method P)	¹ H NMR (400 MHz, DMSO- d_6) δ 8.12 (s, 1 H), 8.05 (s, 1 H), 7.96 (s, 1 H), 7.65 (s, 1 H), 5.26 - 5.36 (m, 1 H), 5.00 - 5.15 (m, 2 H), 4.48 - 4.61 (m, 2 H), 4.18 (br s, 1 H), 3.62 (br d, $J = 13.26$ Hz, 1 H), 3.24 (br d, $J = 13.38$ Hz, 3 H), 2.69 - 2.78 (m, 1 H), 2.51 - 2.58 (m, 1 H), 2.44 (dd, $J = 13.01, 2.25$

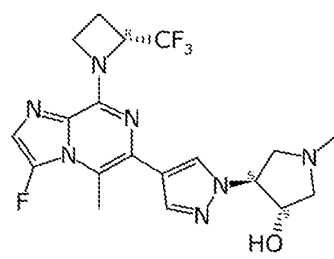
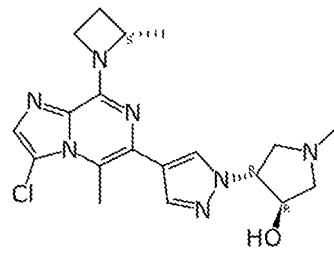
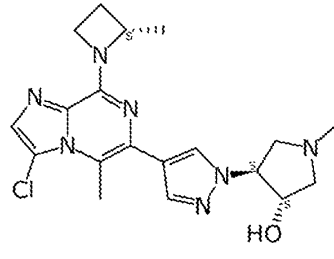
				Hz, 1 H), 1.22 (d, $J=6.63$ Hz, 3 H), 1.07 (d, $J=6.63$ Hz, 3 H)
A118		536.87	m/z 537.2 (M+H)⁺, RT: 2.913 min (Method O)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.10 (s, 1 H), 8.02 (d, $J = 5.13$ Hz, 2 H), 7.53 (s, 1 H), 5.34 - 5.44 (m, 1 H), 5.17 - 5.34 (m, 2 H), 4.97 - 5.08 (m, 1 H), 4.64 - 4.69 (m, 1 H), 4.49 - 4.57 (m, 1 H), 3.84 (br d, $J = 13.01$ Hz, 1 H), 3.40 - 3.49 (m, 1 H), 3.37 (br d, $J = 14.63$ Hz, 1 H), 2.99 - 3.11 (m, 2 H), 2.75 - 2.91 (m, 1 H), 2.67 - 2.74 (m, 1 H), 2.55 - 2.65 (m, 1 H)
A119		536.87	m/z 537.2 (M+H)⁺, RT: 2.932 min (Method O)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.10 (s, 1 H), 8.02 (s, 2 H), 7.54 (s, 1 H), 5.34 - 5.41 (m, 1 H), 5.20 - 5.33 (m, 2 H), 4.96 - 5.03 (m, 1 H), 4.63 - 4.68 (m, 1 H), 4.50 - 4.56 (m, 1 H), 3.85 (br d, $J = 13.38$ Hz, 1 H), 3.41 - 3.51 (m, 1 H), 3.36 (br d, $J = 14.26$ Hz, 1 H), 2.99 - 3.10 (m, 2 H), 2.78 - 2.90 (m, 1 H), 2.67 - 2.73 (m, 1 H), 2.57 - 2.64 (m, 1 H)
A120		421.43	m/z 422.0 (M+H)⁺, RT: 1.781 min (Method F) (3S,4S) absolute stereochemistry	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.10 (s, 1 H) 7.88 - 7.94 (m, 2 H) 7.66 (d, $J=1.10$ Hz, 1 H) 5.28 (dt, $J=8.96, 6.46$ Hz, 1 H) 4.65 - 4.78 (m, 2 H) 4.58 (dt, $J=6.60, 4.28$ Hz, 1 H) 4.37 - 4.46 (m, 1 H) 3.23 (dd, $J=10.09, 8.13$

			assigned arbitrarily	Hz, 1 H) 3.07 (dd, J=10.15, 6.72 Hz, 1 H) 2.98 (dd, J=10.21, 6.54 Hz, 1 H) 2.70 (s, 4 H) 2.57 - 2.69 (m, 2 H) 2.43 (s, 3 H)
A121		421.43	m/z 422.0 (M+H) ⁺ , RT: 1.777 min (Method F) (3R,4R) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.08 (s, 1 H) 7.86 - 7.92 (m, 2 H) 7.63 (d, J=0.86 Hz, 1 H) 5.25 (dt, J=8.83, 6.53 Hz, 1 H) 4.62 - 4.75 (m, 2 H) 4.56 (dt, J=6.48, 4.34 Hz, 1 H) 4.38 (br d, J=7.58 Hz, 1 H) 3.21 (dd, J=9.90, 8.19 Hz, 1 H) 3.05 (dd, J=10.09, 6.66 Hz, 1 H) 2.96 (dd, J=10.09, 6.54 Hz, 1 H) 2.67 - 2.71 (m, 4 H) 2.55 - 2.66 (m, 2 H) 2.41 (s, 3 H)
A122		441.84	442.1 (M+H) ⁺ , RT: 2.431 min (Method O) (3R,4R) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.21 (s, 1 H) 8.01 (d, J = 2.38 Hz, 2 H) 7.53 (s, 1 H) 5.24 - 5.33 (m, 1 H) 4.65 - 4.70 (m, 2 H) 4.49 - 4.56 (m, 2 H) 3.20 (br dd, J = 9.88, 8.13 Hz, 1 H) 3.05 (dd, J = 10.07, 6.69 Hz, 1 H) 2.95 (dd, J = 10.07, 6.32 Hz, 1 H) 2.65 - 2.74 (m, 2 H) 2.57 - 2.63 (m, 1 H) 2.41 (s, 3 H)
A123		441.84	m/z 442.1 (M+H) ⁺ , RT: 2.382 min (Method O) (3S,4S) absolute	¹ H NMR (400 MHz, METHANOL-d ₄) δ 8.21 (s, 1 H) 8.01 (d, J = 4.25 Hz, 2 H) 7.53 (s, 1 H) 5.24 - 5.34 (m, 1 H) 4.64 - 4.71 (m, 2 H) 4.48 - 4.56 (m, 2 H) 3.20 (dd, J = 10.01, 8.13 Hz, 1 H) 3.05

			stereochemistry assigned arbitrarily	(dd, $J = 10.13, 6.75$ Hz, 1 H) 2.94 (dd, $J = 10.13, 6.38$ Hz, 1 H) 2.64 - 2.74 (m, 2 H) 2.56 - 2.64 (m, 1 H) 2.41 (s, 3 H)
A124		421.43	422.3 (M+H) ⁺ , RT: 2.008 min (Method O) (3R,4R) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.19 (s, 1 H) 8.13 (s, 1 H) 7.96 (s, 1 H) 7.36 (s, 1 H) 5.46 (d, $J = 5.25$ Hz, 1 H) 5.23 - 5.33 (m, 1 H) 4.54 - 4.60 (m, 1 H) 4.50 (td, $J = 8.47, 2.69$ Hz, 1 H) 4.40 - 4.48 (m, 1 H) 4.37 (dt, $J = 10.47, 5.08$ Hz, 1 H) 2.97 - 3.03 (m, 1 H) 2.93 (dd, $J = 9.51, 6.75$ Hz, 1 H) 2.78 (dd, $J = 9.63, 5.63$ Hz, 1 H) 2.63 - 2.70 (m, 1 H) 2.46 (s, 3 H) 2.43 - 2.45 (m, 1 H) 2.28 (s, 3 H)
A125		421.43	422.3 (M+H) ⁺ , RT: 1.979 min (Method O) (3S,4S) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.19 (s, 1 H) 8.13 (s, 1 H) 7.96 (s, 1 H) 7.36 (s, 1 H) 5.45 (d, $J = 5.25$ Hz, 1 H) 5.23 - 5.33 (m, 1 H) 4.54 - 4.59 (m, 1 H) 4.50 (br dd, $J = 8.69, 5.57$ Hz, 1 H) 4.41 - 4.48 (m, 1 H) 4.36 (dt, $J = 10.19, 4.91$ Hz, 1 H) 3.00 (t, $J = 8.69$ Hz, 1 H) 2.92 (dd, $J = 9.51, 6.75$ Hz, 1 H) 2.79 (dd, $J = 9.57, 5.69$ Hz, 1 H) 2.63 - 2.72 (m, 1 H) 2.46 (s, 3 H) 2.43 (br d, $J = 4.88$ Hz, 1 H) 2.28 (s, 3 H)

A126		367.46	m/z 368.2 (M+H)⁺, RT: 1.018 min (Method O) (3R,4R) absolute stereochemistry assigned arbitrarily	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.14 (s, 1 H), 7.96 (s, 1 H), 7.75 (s, 1 H), 7.25 (s, 1 H), 4.86 - 4.92 (m, 1 H), 4.69 (ddd, <i>J</i> = 7.57, 6.57, 4.13 Hz, 1 H), 4.50 - 4.59 (m, 2 H), 4.29 - 4.37 (m, 1 H), 3.19 (dd, <i>J</i> = 10.01, 8.13 Hz, 1 H), 3.05 (dd, <i>J</i> = 10.13, 6.63 Hz, 1 H), 2.94 (dd, <i>J</i> = 10.13, 6.38 Hz, 1 H), 2.68 (dd, <i>J</i> = 10.07, 4.57 Hz, 1 H), 2.53 - 2.62 (m, 1 H), 2.45 (s, 3 H), 2.41 (s, 3 H), 2.08 (ddt, <i>J</i> = 10.68, 9.11, 6.49, 6.49 Hz, 1 H), 1.62 (d, <i>J</i> = 6.13 Hz, 3 H)
A127		367.46	LCMS (ESI+): m/z 368.3 (M+H)⁺, RT: 0.699 min (Method O) (3S,4R) absolute stereochemistry assigned arbitrarily	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.15 (s, 1 H), 7.97 (s, 1 H), 7.75 (s, 1 H), 7.26 (s, 1 H), 4.86 - 4.92 (m, 1 H), 4.66 - 4.71 (m, 1 H), 4.51 - 4.59 (m, 2 H), 4.30 - 4.37 (m, 1 H), 3.20 (dd, <i>J</i> = 9.88, 8.25 Hz, 1 H), 3.05 (dd, <i>J</i> = 10.07, 6.69 Hz, 1 H), 2.95 (dd, <i>J</i> = 10.07, 6.44 Hz, 1 H), 2.68 (dd, <i>J</i> = 10.13, 4.50 Hz, 1 H), 2.54 - 2.62 (m, 1 H), 2.46 (s, 3 H), 2.41 (s, 3 H), 2.04 - 2.12 (m, 1 H), 1.62 (d, <i>J</i> = 6.25 Hz, 3 H)
A128		425.39	m/z 426.3 (M+H)⁺, RT: 1.919 min (Method P)	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.17 (s, 1H), 7.98 (s, 1H), 7.95 (s, 1H), 7.21 (d, <i>J</i> = 7.0 Hz, 1H), 5.34 - 5.25 (m, 1H), 4.70 - 4.63 (m,

			(3R,4R) absolute stereochemistry assigned arbitrarily	2H), 4.55 - 4.48 (m, 2H), 3.19 (dd, $J = 8.0, 10.0$ Hz, 1H), 3.04 (dd, $J = 6.6, 10.1$ Hz, 1H), 2.94 (dd, $J = 6.4, 10.1$ Hz, 1H), 2.77 - 2.69 (m, 1H), 2.68 - 2.64 (m, 1H), 2.63 - 2.55 (m, 1H), 2.40 (s, 3H)
A129		425.39	m/z 426.2 (M+H) ⁺ , RT: 1.914 min (Method P) (3S,4S) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.17 (s, 1H), 7.98 (s, 1H), 7.95 (s, 1H), 7.21 (d, $J = 7.0$ Hz, 1H), 5.33 - 5.22 (m, 1H), 4.71 - 4.62 (m, 2H), 4.55 - 4.48 (m, 2H), 3.19 (dd, $J = 8.0, 10.1$ Hz, 1H), 3.04 (dd, $J = 6.6, 10.0$ Hz, 1H), 2.93 (dd, $J = 6.4, 10.1$ Hz, 1H), 2.78 - 2.69 (m, 1H), 2.69 - 2.64 (m, 1H), 2.63 - 2.56 (m, 1H), 2.40 (s, 3H)
A130		439.42	m/z 440.3 (M+H) ⁺ , RT: 1.943 min (Method P) (3R,4R) absolute stereochemistry assigned arbitrarily	¹ H NMR (400 MHz, METHANOL- <i>d</i> ₄) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.24 (d, $J = 6.8$ Hz, 1H), 5.28 - 5.16 (m, 1H), 4.73 - 4.68 (m, 1H), 4.62 (dt, $J = 5.6, 8.7$ Hz, 1H), 4.55 (td, $J = 4.3, 6.6$ Hz, 1H), 4.46 - 4.38 (m, 1H), 3.21 (dd, $J = 8.1, 10.1$ Hz, 1H), 3.05 (dd, $J = 6.6, 10.1$ Hz, 1H), 2.95 (dd, $J = 6.4, 10.1$ Hz, 1H), 2.76 (d, $J = 5.4$ Hz, 3H), 2.71 - 2.61 (m, 2H), 2.60 - 2.53 (m, 1H), 2.41 (s, 3H)

A131		439.42	m/z 440.2 (M+H)⁺, RT: 1.946 min (Method P) (3S,4S) absolute stereochemistry assigned arbitrarily	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 8.04 (s, 1H), 7.86 (s, 1H), 7.23 (d, J = 6.8 Hz, 1H), 5.27 - 5.17 (m, 1H), 4.70 (dt, J = 4.1, 7.1 Hz, 1H), 4.62 (dt, J = 5.6, 8.5 Hz, 1H), 4.55 (td, J = 4.4, 6.5 Hz, 1H), 4.46 - 4.38 (m, 1H), 3.20 (dd, J = 8.3, 9.8 Hz, 1H), 3.04 (dd, J = 6.6, 10.1 Hz, 1H), 2.95 (dd, J = 6.5, 10.0 Hz, 1H), 2.76 (d, J = 5.4 Hz, 3H), 2.71 - 2.61 (m, 2H), 2.60 - 2.53 (m, 1H), 2.41 (s, 3H)
A132		401.90	m/z 402.3 (M+H)⁺, RT: 1.792 min (Method O) (3R,4R) absolute stereochemistry assigned arbitrarily	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 7.98 (s, 1H), 7.77 (s, 1H), 7.41 (s, 1H), 4.8- 4.9 (m, 1H), 4.7-4.7 (m, 1H), 4.5-4.6 (m, 1H), 4.4-4.5 (m, 1H), 4.2-4.3 (m, 1H), 3.20 (br t, 1H, J = 9.0 Hz), 3.04 (br dd, 1H, J = 6.9, 9.9 Hz), 2.95 (br dd, 1H, J = 6.6, 9.9 Hz), 2.88 (s, 3H), 2.68 (br dd, 1H, J = 4.5, 10.0 Hz), 2.5-2.6 (m, 1H), 2.40 (s, 3H), 2.0-2.1 (m, 1H), 1.58 (br d, 3H, J = 6.1 Hz)
A133		401.90	m/z 402.3 (M+H)⁺, RT: 1.816 min (Method O) (3S,4S) absolute stereochemistry	¹H NMR (400 MHz, METHANOL-<i>d</i>₄) δ 7.98 (s, 1H), 7.78 (s, 1H), 7.42 (s, 1H), 4.8-4.9 (m, 1H), 4.70 (ddd, 1H, J = 4.1, 6.6, 7.8 Hz), 4.56 (td, 1H, J = 4.3, 6.6 Hz), 4.49 (dt, 1H, J = 5.5, 9.1 Hz), 4.28 (dt, 1H, J = 6.9, 9.1 Hz), 3.20

			assigned arbitrarily	(dd, 1H, J = 7.9, 10.1 Hz), 3.04 (dd, 1H, J = 6.6, 10.1 Hz), 2.95 (dd, 1H, J = 6.5, 10.1 Hz), 2.89 (s, 3H), 2.68 (dd, 1H, J = 4.6, 10.1 Hz), 2.56 (dtd, 1H, J = 5.4, 8.8, 10.7 Hz), 2.41 (s, 3H), 2.05 (tdd, 1H, J = 6.5, 9.0, 10.8 Hz), 1.58 (d, 3H, J = 6.1 Hz)
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[00682] The utility of the compounds of the present disclosure and the salts of such compounds as medical agents in the treatment of the disease/conditions described herein in mammals (e.g. humans, male or female) is demonstrated by the activity and advantages of the compounds of the present disclosure in one or more of the conventional assays and in vivo assays described and noted herein. The in vivo assays (with appropriate modifications within the skill in the art) can be used to determine the activity of other agents as well as the compounds of the present disclosure. Thus, the protocols described herein can also be used to demonstrate the utility of the combinations of the compounds of the present disclosure. The assays and models may also demonstrate particular other property advantages e.g., side effect profile; half-life. In addition, such assays provide a means whereby the activities of the compounds of the present disclosure and the salts of such compounds (or the other agents described herein) can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

[00683] Absorption, Distribution, Metabolism and Excretion (ADME) and pharmacokinetics (PK) of compounds and exemplary assays are discussed in the on-line publication by Thomas D. Y. Chung, David B. Terry and Layton H. Smith “In Vitro and In Vivo Assessment of ADME and PK Properties During Lead Selection and Lead Optimization- Guidelines, Benchmarks and Rules of Thumb—(<https://www.ncbi.nlm.nih.gov/books/NBK326710/>).

[00684] Animal models of nonalcoholic fatty liver disease are described in Nutrients, 2017 Oct; 9(10): 1072; Int. J. Mol. Sci. 2022, 23, 15791 and Digestion 2020; 101:522-535. Animal models of fructose inhibition are described in Molecular Metabolism, 2021; 48:101196.

EXAMPLE 27: KHK Inhibition Assays

[00685] Determination of Human and Rat recombinant KHK-A and KHK-C isozyme IC₅₀ Values

[00686] An assay reagent cocktail was prepared by combining NADH, water, TEA, KCl, MgCl₂, PEP, ATP, DTT, coupling enzymes (pyruvate kinase and lactate dehydrogenase, LDH) to final concentrations as shown in Table E.

TABLE E

Reagent	Final Concentration
NADH	300 μM

Reagent	Final Concentration
Water	–
TEA	33 mM
KCl	100 mM
MgCl ₂	6 mM
PEP	1.33 mM
ATP	0.1 mM
DTT	12 mM
Pyruvate kinase	1.0 U/mL
LDH	1.0 U/mL

[00687] To this was added the relevant KHK isozyme to a final concentration of 6 nM. Aliquots of each inhibitor compound were diluted via 5-fold serial dilutions to produce final concentrations ranging from 1000 nM to 0.064 nM. The inhibitor aliquots were added to the assay reagent cocktail containing KHK with fructose (at a concentration of 2 mM) in a 96-well plate. The absorbance at 340nm was measured via spectrophotometry and inhibition was analyzed using non-linear regression.

[00688] Results of the assay are presented in Table F.

TABLE F

Compound	Human KHK-C IC50 (nM)	Human KHK-A IC50 (nM)	Rat KHK-C IC50 (nM)	Rat KHK-A IC50 (nM)
A1	289	120	136	59.4
A2	347	640	380	112
A3	291	N/A	N/A	N/A
A4	9	10	18	6.7
A5	11.5	32	30	16
A6	3.5	5.6	19.6	3
A7	89.9	N/A	N/A	N/A
A8	22.9	N/A	N/A	N/A
A9	5.9	15	22	12
A10	68.7	39	50	22
A11	1.4	3.7	6.7	5.2
A12	8.9	4.7	8.7	3.1
A13	14.6	22	47	17
A14	29.1	N/A	N/A	N/A
A15	29	N/A	N/A	N/A
A16	4.5	1.5	12	4.2
A17	3.7	4.6	20	7.2
A18	4.7	5.1	13.2	4.9

Compound	Human KHK-C IC50 (nM)	Human KHK-A IC50 (nM)	Rat KHK-C IC50 (nM)	Rat KHK-A IC50 (nM)
A19	10.5	8.5	22	8.7
A20	18.7	14	37	20
A21	3.9	1.3	14	4
A22	551	N/A	N/A	N/A
A23	35.9	N/A	N/A	N/A
A24	199	N/A	N/A	N/A
A25	153	N/A	N/A	N/A
A26	71	N/A	N/A	N/A
A27	130	N/A	N/A	N/A
A28	73.9	N/A	N/A	N/A
A29	5.9	4.9	6.1	4.1
A30	300	N/A	N/A	N/A
A31	8.7	4.6	3.3	2.7
A32	239	N/A	N/A	N/A
A33	11.5	N/A	N/A	N/A
A34	13.4	N/A	N/A	N/A
A35	22.5	N/A	N/A	N/A
A36	50.2	N/A	N/A	N/A
A37	5.9	6.6	16	4.8
A38	2.1	2.9	5	1.2
A39	1.8	1.2	5.6	2.4
A40	3.2	N/A	N/A	N/A
A41	33.5	N/A	N/A	N/A
A42	9.7	7.2	11	8.2
A43	1.5	2.9	7.6	4.3
A44	52.3	N/A	N/A	N/A
A45	5.3	13	21	7.4
A46	10.5	27	48	22
A47	158	N/A	N/A	N/A
A48	3.4	3	12	4.5
A49	7.4	12	24	14
A50	17.9	20	25	16
A51	3.0	N/A	N/A	N/A

Compound	Human KHK-C IC50 (nM)	Human KHK-A IC50 (nM)	Rat KHK-C IC50 (nM)	Rat KHK-A IC50 (nM)
A52	6.4	1.9	21	7.3
A53	39.1	N/A	N/A	N/A
A54	25.9	N/A	N/A	N/A
A55	66	N/A	N/A	N/A
A56	78.5	N/A	N/A	N/A
A57	14.6	11	29	11
A58	14.5	7.4	10	5.2
A59	56.2	N/A	N/A	N/A
A60	17.4	19	17	14
A61	20.9	95	85	46
A62	4.9	8.1	36	10.5
A63	24.3	N/A	N/A	N/A
A64	35.5	N/A	N/A	N/A
A65	4.6	4	52	7.7
A66	15.5	2	11	7.2
A67	13.3	13	43	13
A68	7.1	9.8	21	4.1
A69	4.7	2.3	3	4.9
A70	0.9	1.8	3.8	0.3
A71	4.3	1.2	7.7	2.5
A72	31.9	N/A	N/A	N/A
A73	26.7	N/A	N/A	N/A
A74	188	N/A	N/A	N/A
A75	531	N/A	N/A	N/A
A76	10.4	N/A	N/A	N/A
A77	25	N/A	N/A	N/A
A78	27.9	N/A	N/A	N/A
A79	72.4	N/A	N/A	N/A
A80	4.3	N/A	N/A	N/A
A81	23.1	N/A	N/A	N/A
A82	18.4	N/A	N/A	N/A
A83	5.6	N/A	N/A	N/A
A84	5.9	N/A	N/A	N/A

Compound	Human KHK-C IC50 (nM)	Human KHK-A IC50 (nM)	Rat KHK-C IC50 (nM)	Rat KHK-A IC50 (nM)
A85	300	N/A	N/A	N/A
A86	55.8	N/A	N/A	N/A
A87	11.6	N/A	N/A	N/A
A88	52.8	N/A	N/A	N/A
A89	3.2	5.8	15	5.5
A90	123	N/A	N/A	N/A
A91	92.9	N/A	N/A	N/A
A92	43.8	N/A	N/A	N/A
A93	94.9	N/A	N/A	N/A
A94	482	N/A	N/A	N/A
A95	37.2	N/A	N/A	N/A
A96	164	N/A	N/A	N/A
A97	197	N/A	N/A	N/A
A98	14.3	7.3	11	5
A99	52	N/A	N/A	N/A
A100	20.6	N/A	N/A	N/A
A101	119	N/A	N/A	N/A
A102	44.4	N/A	N/A	N/A
A103	118	N/A	N/A	N/A
A104	29.5	N/A	N/A	N/A
A105	24.9	N/A	N/A	N/A
A106	50	N/A	N/A	N/A
A107	76.6	N/A	N/A	N/A
A109	27.8	N/A	N/A	N/A
A109	27.1	N/A	N/A	N/A
A110	14.1	10.7	6.1	4
A111	12.7	4.5	6.1	2.6
A112	43.8	N/A	N/A	N/A
A113	22.5	N/A	N/A	N/A
A114	6.2	4.2	5.2	4.3
A115	7.4	7.4	7.3	2.7
A116	6.6	N/A	N/A	N/A
A117	5.8	N/A	N/A	N/A

Compound	Human KHK-C IC50 (nM)	Human KHK-A IC50 (nM)	Rat KHK-C IC50 (nM)	Rat KHK-A IC50 (nM)
A118	158	N/A	N/A	N/A
A119	134	N/A	N/A	N/A
A120	5.3	9.1	24.0	7.0
A121	8.8	N/A	N/A	N/A
A122	4.4	N/A	N/A	N/A
A123	4.1	2.4	4.0	2.4
A124	11.4	N/A	N/A	N/A
A125	10.5	7.2	36	11
A126	42.0	N/A	N/A	N/A
A127	40.9	N/A	N/A	N/A
A128	18.8	N/A	N/A	N/A
A129	21.3	N/A	N/A	N/A
A130	3.7	4.05	20	6.8
A131	5.3	N/A	N/A	N/A
A132	10.3	N/A	N/A	N/A
A133	11.9	N/A	N/A	N/A

EXAMPLE 28: Cell-based Potency Assay (HepG2 assay)

[00689] Testing inhibition effect of compounds against human KHK in HepG2 Cells

[00690] HepG2 cells were grown in RPMI 1640 supplemented media on 100 mm plates to near confluency (about $5-8 \times 10^6$ cells). The growth media was aspirated and 4 mL trypsin solution (0.25% (w/v) + 0.25% (w/v) EDTA) was added, followed by incubation at 37 °C for 5-10 mins. The cells were pelleted and resuspended in 2 mL complete media.

[00691] The cells were then placed in a 96 well plate at 20,000-50,000 cells per well and grown for 20-28 hours at 37 °C to allow adherence.

[00692] Inhibitor compounds were diluted in DMSO to 50 μ M, then serially diluted with MEM media (ThermoFisher). Final inhibitor concentration ranged from 1000 nM to 0.064 nM (5-fold dilution series).

[00693] The RPMI medium was removed from the plate of confluent cells. The plate was then incubated for 35 min at 37 °C, after which were added 0.1 mL of the diluted inhibitor compounds in MEM with fructose, 0.1 mL of MEM media without inhibitor compound or fructose, or trypsin; yielding a final concentration of fructose at 20 mM. The plate was subsequently incubated for 20 min at 37 °C, then placed on ice to stop the reactions.

[00694] Next, 200 μ L of cold 80% (v/v) methanol:water was added to all wells, except the controls used to enumerate cell count. The plate was vortexed and cell debris removed by centrifugation. To measure F1P produced, the resulting supernatant fraction was analyzed by LC/MS.

[00695] IC50 data is presented in Table G.

TABLE G

Compound	HepG2 IC50 (nM)
C1	160
C2	91
C3	4
A5	36.1
A6	6.5
A9	17.3
A10	203
A11	2.4
A12	21.1
A18	3.5
A19	25.4
A20	44.4
A21	3.8
A29	6.8
A39	2.4
A42	11.3
A43	1.3
A45	13.3
A46	39.6
A49	8.6
A50	25
A57	44.9
A58	24
A60	18.2
A62	9.3
A65	13.2
A66	20.9
A67	21.7
A89	8.2
A98	26.3

The structures of compounds C1-C3 are provided in paragraph [00705].

EXAMPLE 29: Cell-based Potency Assay (KHK-C-overexpressing HepG2 assay)

[00696] Testing inhibition effect of compounds against human KHK-C in engineered HepG2 cells.

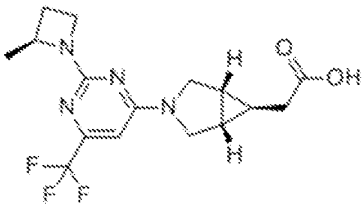
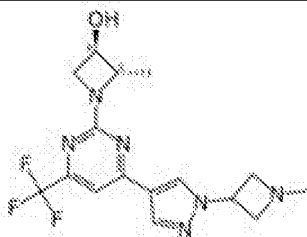
[00697] Engineered HepG2 cells were generated using methods known to those of skill in the art. Briefly, HepG2 cells were incubated with lentivirus carrying a transgene encoding human KHK-C, and grown under antibiotic selection.

[00698] KHK-C-overexpressing HepG2 cells were grown in RPMI1640 supplemented media on T-182 cm² flask to near confluency (about 25-40 x10⁶ cells). The growth media was aspirated, the flask was washed with 10mL PBS, and 4 mL trypsin solution (0.25% (w/v) + 0.25% (w/v) EDTA) was added, followed by incubation at 37 °C for 3-5 mins. The cells were pelleted and resuspended in 2 mL complete media.

[00699] The cells were then placed in a 96-well plate at 20,000-40,000 cells per well and grown for 20-28 hours at 37 °C to allow adherence.

[00700] Inhibitor compounds were diluted in DMSO to 50 µM, then serially diluted with MEM media (ThermoFisher). Final inhibitor concentration ranged from 5000 nM to 0.32 nM. Control compounds C1, C2, and C3 were tested for comparison with compounds disclosed herein.

TABLE H

Control Compound	Structure
C1 (also called PF-06835919, WO2017/115205 Ex. 49)	
C2 (also called LY3522348, WO2020/257171 Ex. 1)	
C3 (WO2020/257171-Ex. 35)	

[00701] The RPMI medium was removed from the plate of confluent cells. The plate was then incubated for 35 min at 37 °C with 0.1mL of the diluted inhibitor compounds in MEM. After, an additional 0.1mL of the diluted inhibitor compounds in MEM with fructose, or 0.1 mL of MEM media without inhibitor compound and/or fructose; yielding a final

concentration of fructose at 30 mM was added. The plate was subsequently incubated for 5 min at 37 °C, then placed on ice to stop the reactions.

[00702] Next, 200 μ L of cold 80% (v/v) methanol:water was added to all wells and placed in the -80 °C freezer for 1 hour with an adhesive seal. The plate was vortexed and cell debris removed by centrifugation. To measure F1P produced, the resulting supernatant fraction was analyzed by LC/MS.

[00703] IC₅₀ data is presented in Table I.

TABLE I

Compound	KHK-C overexpressing HepG2, geomean IC ₅₀ (nM)
C1	536
C2	457
C3	191
A6	39
A9	70.9
A11	24.6
A18	53.5
A21	40.1
A29	46.5
A39	64.4
A42	96
A43	46.5
A45	21.8
A46	112
A49	67
A60	69.6
A62	167
A89	36.4
A120	190
A123	71
A125	59.3
A130	59.9

EXAMPLE 30: CYP Inhibition Assay in Human Liver Microsomes

[00704] Cytochrome P450 inhibition profiling

[00705] A potential limitation of novel drugs for metabolic diseases is the risk of drug-drug interactions mediated by inhibition of the cytochrome P450 (CYP) enzymes that contribute to xenobiotic metabolism, including CYP1A2, CYP2C9, CYP2C8, CYP2D6, and CYP3A4, among others. Frequent concomitant medications in patients suffering from metabolic disease, type 2 diabetes, obesity, hypertension, and/or MASLD/MASH include a number of substrates, inhibitors, or inducers of the CYP enzymes, including HMG-CoA reductase inhibitors (statins), thiazolidinediones, fibrates, sulfonyleureas, selective serotonin reuptake inhibitors, angiotensin II receptor blockers. Total exposure of these drugs may be affected if they are coadministered with an inhibitor of CYP enzymes. Therefore, lack of meaningful inhibition of CYP enzymes, alongside maintained potency as an inhibitor of KHK-C and KHK-A, is a desirable characteristic for a clinical candidate. Preferred compounds of this disclosure have beneficial properties i.e., lacking significant CYP inhibition.

[00706] Testing inhibition of compounds against CYP enzymes

[00707] Human liver microsomes (HLMs) were incubated with known substrates of specific CYP enzymes (for example, phenacetin for CYP1A2; diclofenac for CYP2C9; S-mephenytoin for CYP2C19; dextromethorphan for CYP2D6; midazolam for CYP3A4). Substrate metabolism to the known metabolite was monitored by LC-MS-MS. Positive control inhibitors were tested at a single concentration, and test compounds were tested in a 7-point dose-response curve starting from a high concentration of 50 μ M with ~3-fold dilution series to a low concentration of 50 nM.

[00708] Each assay well contained 0.2 mg/mL HLMs, 1mM NADPH, substrate-dependent final concentration of each substrate, and specified concentration of either positive control inhibitor or test compound. Wells were incubated for 10 minutes at 37 °C and reactions were stopped by adding cold stop solution (for example, 200ng/mL tolbutamide in acetonitrile) followed by centrifugation at 4000 rpm for 20 minutes to precipitate protein. Supernatant was added to 0.5-volume of HPLC water, shaken for 10 minutes, and analyzed by LC-MS-MS.

EXAMPLE 31: hERG Inhibition Assay by Automated Patch Clamp Method

[00709] An additional potential limitation of novel drugs is the risk of cardiotoxicity mediated by binding to or inhibition of cardiac ion channels, including for example hERG (human ether-a-go-go-related gene). hERG is a subunit of a potassium channel that mediates cardiac repolarization, and is inhibited by diverse classes of small molecules, which may lead to arrhythmias. Therefore, maximizing the window between potency as an inhibitor of the target enzyme, ketohexokinase, and the potency as an inhibitor of hERG is a desirable characteristic for a clinical candidate. Preferred compounds of this disclosure have beneficial properties i.e., lacking significant hERG inhibition and/or a large window between KHK inhibitor potency and hERG inhibitor potency.

[00710] Testing inhibition of compounds against hERG (human ether-a-go-go-related gene)

[00711] CHO cells stably expressing hERG channels were seeded in ~298 mOsm 10mM HEPES buffer, pH 7.4 containing 140mM NaCl, 4mM KCl, 2mM CaCl₂, 5mM glucose on the Nanion SyncroPatch 384PE for profiling using the automated patch clamp method.

[00712] Positive control (amitriptyline) and test compounds were tested in a 5-point dose-response curve starting from a high concentration of 30 μ M with ~3-fold dilution series to a low concentration of 300 nM.

[00713] Currents were elicited using a voltage command protocol consisting of a continuous holding potential of -80 mV, first stepped to -50 mV for 80 msec for leak subtraction, then stepped to +20 mV for 4,800 msec to open hERG channels, then stepped to -50 mV for 5,000 msec causing a hERG "tail current" that was measured and collected for analysis, then stepped to the holding potential of -80 mV for 1,000 msec. This command protocol was repeated every 20 seconds, continuously during the assay (300 seconds before addition of control or test compound, and 300 seconds following addition of control or test compound).

EXAMPLE 32: Steady-State Kinetics

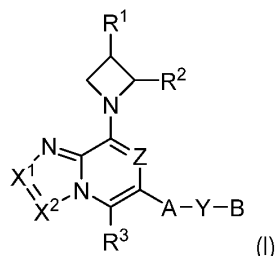
[00714] An additional potential limitation of novel drugs inhibiting ketohexokinase isoforms is the risk that increasing concentrations of substrate (for example, fructose and/or ATP) diminish the potency of the drugs due to a competitive mode of inhibition. Inhibition of ketohexokinase metabolism of fructose to fructose-1-phosphate is expected to increase the concentration of both ATP and fructose, potentially to an extent that may outcompete the novel drug as a competitive inhibitor. Therefore, noncompetitive modes of inhibition of the target enzyme, i.e., where potency as an enzyme inhibitor is not affected by the concentration of any enzyme substrate, may be a desirable characteristic for a clinical candidate. Mode of inhibition may be determined through a series of steady state kinetics experiments, performed as known by one skilled in the art, for example as described in Copeland, RA, Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists (2013), where compound potency as an inhibitor of ketohexokinase is determined across a range of substrate concentrations, i.e., varying concentration of ATP in excess of fructose; or varying concentration of fructose in excess of ATP. Preferred compounds of this disclosure have beneficial properties with respect to the mode of inhibition, whereby increased ATP and/or fructose concentrations do not impact compound potency as an inhibitor of ketohexokinase.

[00715] All references provided herein are incorporated herein in their entirety by reference. As used herein, all abbreviations, symbols and conventions are consistent with those used in the contemporary scientific literature. See, e.g., Janet S. Dodd, ed., The ACS Style Guide: A Manual for Authors and Editors, 2nd Ed., Washington, D.C.: American Chemical Society, 1997.

[00716] It is to be understood that while the disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A compound having a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein

each of X¹ and X² is independently N or CR⁴;

Z is N or CR⁵;

R¹ is H or OH;

R² is C₁₋₆alkyl or C₁₋₆haloalkyl;

R³ is H, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₁₋₆alkoxy;

R⁴ is H, halo, C₁₋₆alkyl, C₁₋₆haloalkyl, or C₃₋₁₀ cycloalkyl;

R⁵ is H, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl;

Y is a bond or C₁₋₆alkylene-C(O);

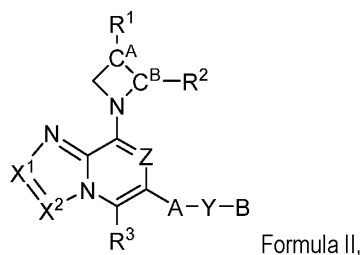
A is 5- or 6-membered heteroaryl having 1 to 3 ring nitrogen atoms, wherein the heteroaryl is optionally substituted with 1 or 2 R⁶;

B is 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, wherein the heterocycloalkyl is optionally substituted with 1 or 2 R⁶;

each R⁶ independently is OH, halo, CN, -N(R^a)(R^b), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆hydroxyalkyl, or C₁₋₆alkoxy; and

R^a and R^b are independently H or C₁₋₃alkyl.

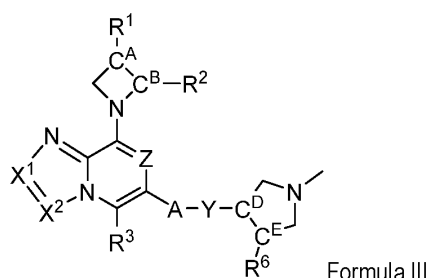
2. The compound or salt of claim 1, having the structure of Formula II:



wherein C^A and C^B each represent a carbon stereocenter.

3. The compound or salt of claim 2, wherein C^A is a carbon in the R configuration and C^B is a carbon in the R configuration.

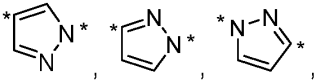
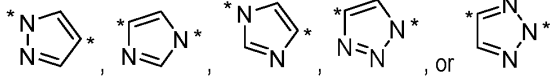
4. The compound or salt of claim 2, wherein C^A is a carbon in the R configuration and C^B is a carbon in the S configuration.
5. The compound or salt of claim 1, having the structure of Formula III:



wherein C^A, C^B, C^D and C^E each represent a carbon stereocenter.

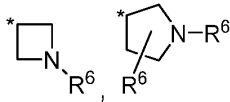
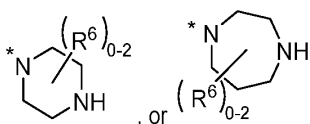
6. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration and C^D and C^E are carbons in the R configuration,
7. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration and C^D and C^E are carbons in the S configuration.
8. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, C^D is a carbon in the R configuration and C^E is a carbon in the S configuration.
9. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the R configuration, C^D is a carbon in the S configuration and C^E is a carbon in the R configuration.
10. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration and C^D and C^E are carbons in the R configuration,
11. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration and C^D and C^E are carbons in the S configuration.
12. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the R configuration and C^E is a carbon in the S configuration.
13. The compound or salt of claim 5, wherein C^A is a carbon in the R configuration, C^B is a carbon in the S configuration, C^D is a carbon in the S configuration and C^E is a carbon in the R configuration.
14. The compound or salt of any one of claims 1 to 13, wherein one of X¹ and X² is N and the other is CR⁴.
15. The compound or salt of claim 14, wherein X¹ is N and X² is CR⁴.
16. The compound or salt of claim 14, wherein X¹ is CR⁴ and X² is N.
17. The compound or salt of any one of claims 1 to 16, wherein R⁴ is H, halo, C₁₋₆alkyl, or C₁₋₆haloalkyl.
18. The compound or salt of claim 17, wherein R⁴ is H, C₁₋₆alkyl, or C₁₋₆haloalkyl.

19. The compound or salt of claim 17 or 18, wherein R⁴ is H, methyl, or CF₃.
20. The compound or salt of claim 17, wherein R⁴ is halo.
21. The compound or salt of claim 20, wherein R⁴ is fluoro.
22. The compound or salt of any one of claims 1 to 16, wherein R⁴ is C₃₋₁₀ cycloalkyl.
23. The compound or salt of claim 22, wherein R⁴ is cyclopropyl.
24. The compound or salt of any one of claims 1 to 23, wherein Z is N.
25. The compound or salt of any one of claims 1 to 23, wherein Z is CR⁵.
26. The compound or salt of any one of claims 1 or 14 to 25, wherein R¹ is H.
27. The compound or salt of any one of claims 1 to 25, wherein R¹ is OH.
28. The compound or salt of any one of claims 1 to 27, wherein R² is C₁₋₆alkyl.
29. The compound or salt of claim 28, wherein R² is methyl.
30. The compound or salt of any one of claims 1 to 27, wherein R² is C₁₋₆haloalkyl.
31. The compound or salt of claim 30, wherein R² is CHF₂ or CF₃.
32. The compound or salt of any one of claims 1 to 31, wherein R³ is H or C₁₋₆alkyl.
33. The compound or salt of claim 32, wherein R³ is H or methyl.
34. The compound or salt of any one of claims 1 to 33, wherein A is a 5-membered heteroaryl having 1 to 3 ring nitrogen atoms, and is optionally substituted with 1 or 2 R⁶.
35. The compound or salt of claim 34, wherein A is pyrazolyl, imidazolyl, or triazolyl, and is optionally substituted with 1 or 2 R⁶.
36. The compound or salt of claim 34 or 35, wherein A is unsubstituted.

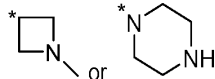
37. The compound or salt of any one of claims 34 to 36, wherein A is , , or , each * indicates a point of attachment to the rest of the compound, and A is optionally substituted with 1 or 2 R⁶.

38. The compound or salt of any one of claims 1 to 37, wherein Y is a bond.
39. The compound or salt of any one of claims 1 to 37, wherein Y is C₁₋₆alkylene-C(O).
40. The compound or salt of claim 39, wherein Y is C₁alkylene-C(O).

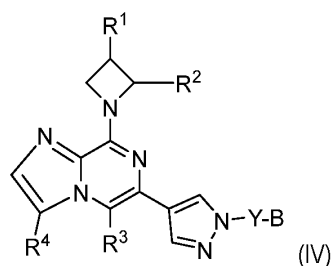
41. The compound or salt of any one of claims 1 to 40, wherein B is a 4- to 8-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R⁶.
42. The compound or salt of any one of claims 1 to 4 or 14 to 41, wherein B is a 4- or 6-membered heterocycloalkyl having 1 or 2 ring nitrogen atoms, and is optionally substituted with 1 or 2 R⁶.
43. The compound or salt of claim 42, wherein B is azetidiny, pyrrolidinyl, piperazinyl, or diazepinyl, and is optionally substituted with 1 or 2 R⁶.
44. The compound or salt of claim 43, wherein B is azetidiny or piperazinyl, and is optionally substituted with 1 or 2 R⁶.
45. The compound or salt of any one of claims 1 to 4 and 14 to 44, wherein B is unsubstituted.
46. The compound or salt of any one of claims 1 to 44, wherein B is substituted with one R⁶.
47. The compound or salt of any one of claims 1 to 44, wherein B is substituted with two R⁶.

48. The compound or salt of any one of claims 1 to 4 or 14 to 41, wherein B is , , and * indicates a point of attachment to the rest of the compound.

49. The compound or salt of any one of claims 46 to 48, wherein at least one R⁶ is C₁₋₆alkyl.
50. The compound or salt of claim 49, wherein at least one R⁶ is methyl.

51. The compound or salt of claim 48, wherein B is .

52. The compound or salt of any one of claims 1-4, 26, and 27, having a structure of Formula (IV):



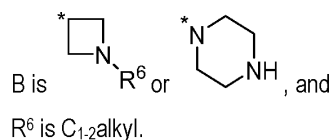
wherein

R⁴ is H, chloro, fluoro or C₁₋₂alkyl,

R² is trifluoromethyl or C₁₋₂alkyl,

R³ is H or C₁₋₂alkyl,

Y is a bond or C₁alkylene-C(O),



53. A compound as recited in Table A, or a pharmaceutically acceptable salt thereof.
54. A compound selected from (2S,3R)-1-{3-chloro-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triaza-7-indenyl}-2-methyl-3-azetidinol (A18);
7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A11);
7-[(S)-2-methyl-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A9);
7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A21);
2-{4-{7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl}-1-(1-piperazinyl)-1-ethanone (A29);
7-[(S)-2-methyl-1-azetidinyl]-3-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3a,6-triazaindene (A49);
2-{4-{7-[(S)-2-methyl-1-azetidinyl]-3-chloro-1,3a,6-triaza-5-indenyl}-1-pyrazolyl}-1-(1-piperazinyl)-1-ethanone (A60); and
7-[(R)-2-(trifluoromethyl)-1-azetidinyl]-4-methyl-5-[1-(1-methyl-3-azetidinyl)-4-pyrazolyl]-1,3,3a,6-tetraazaindene (A89), or a pharmaceutically acceptable salt thereof.
55. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 54 and a pharmaceutically acceptable excipient.
56. A method for inhibiting ketohexokinase (KHK) in a cell comprising contacting the cell with the compound or salt of any one of claims 1 to 54 or the pharmaceutical composition of claim 55.
57. A method for treating or preventing a disease or disorder associated with aberrant ketohexokinase (KHK) activity in a subject comprising administering to the subject a therapeutic amount of the compound or salt of any one of claims 1 to 54 or the pharmaceutical composition of claim 55.
58. The method of claim 57, wherein the disease or disorder is associated with KHK dysregulation.
59. The method of claim 57 or 58, wherein the disease or disorder is metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes mellitus (T2D), diabetic kidney disease (DKD), alcoholic steatohepatitis (ASH), alcohol-associated liver disease (ALD), liver fibrosis or

- cirrhosis, liver disease caused by hepatocellular stress, hereditary fructose intolerance, hyperuricemia, gout, addictive craving, a neurodegenerative disease, or cancer.
60. The method of claim 59, wherein the disease or disorder is NASH or MASH.
61. The method of any one of claims 56 to 60, further comprising administering to the subject a therapeutically effective amount of an additional therapeutic agent.
62. The method of claim 61, wherein the additional therapeutic agent comprises metformin, a fructose transporter inhibitor, an aldose reductase inhibitor, a xanthine oxidase inhibitor, a thyroid hormone beta-receptor agonist, an incretin hormone receptor agonist or modulator, or a sodium/glucose transporter inhibitor.
63. The method of claim 62, wherein the incretin hormone receptor agonist or modulator is semaglutide, dulaglutide, liraglutide, tirzepatide, survodutide, retatrutide, pemvidutide, VK2735, orforglipron, cagrilintide/semaglutide, danuglipron, maridebart cafraglutide, RGT-075, PF-0695422, NN9487, NN9541, CT-388, CT-868, CT-996, efinopegdutide, efocipegtrutide, AZD9550, DR10624, NLY01, ECC5004, mazdutide, exenatide, TERN-601, ecnoglutide, or XW-004.
64. The method of claim 63, wherein the fructose transporter inhibitor is an inhibitor of GLUT2, GLUT5, or both.
65. The method of claim 63, wherein the aldose reductase inhibitor is AT-001, AT-003, gavoirestat, ranirestat, epalrestat, fidarestat, imirestat, tolrestat, or risarestat.
66. A method for treating or preventing metabolic syndrome, hypertriglyceridemia, hypercholesterolemia, non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), non-alcoholic steatohepatitis (NASH), metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes mellitus (T2D), diabetic kidney disease (DKD), alcoholic steatohepatitis (ASH), alcohol-associated liver disease (ALD), liver fibrosis or cirrhosis, liver disease caused by hepatocellular stress, hereditary fructose intolerance, hyperuricemia, gout, addictive craving, a neurodegenerative disease, or cancer in a subject, comprising administering to the subject a therapeutic amount of the compound or salt of any one of claims 1 to 54 or the pharmaceutical composition of claim 55.
67. The method of claim 66, wherein the disease or disorder is NASH or MASH.