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(54) Title: TYK2 INHIBITORS AND COMPOSITIONS AND METHODS THEREOF

(57) Abstract: The invention provides a novel class of therapeutic agents that are safe and effective TYK2 inhibitors and pharmaceutical compositions of these compounds and methods of preparation and use thereof against various TYK2-mediated diseases and disorders.



TYK2 INHIBITORS AND COMPOSITIONS AND METHODS THEREOF

Technical Fields of the Invention

[0001] The invention generally relates to novel compounds and methods for their therapeutic use. More particularly, the invention provides a novel class of tyrosine kinase 2 inhibitors as well as pharmaceutical compositions of these compounds and methods of preparation and use thereof against various diseases and conditions.

Background of the Invention

[0002] Janus kinase (JAK) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the Janus kinase - Signal Transduction Activators of Transcription (JAK-STAT) pathway. There are four members in the JAK family of enzymes in humans, *i.e.*, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). The family is defined by the presence of two adjacent kinase domains, JH1 and JH2, of which JH1 performs the phosphorylation involved in pathway activation whereas JH2 regulates JH1 function. (Thomas, *et al.*, **2015** *British Journal of Cancer* 113, 365–371.)

[0003] These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors such as common gamma-chain receptors and the glycoprotein 130 (gp130) transmembrane proteins. (Murray, *et al.* **2007** *Immunol.* 178(5):2623-2629.) About 40 cytokine receptors signal through combinations of these four JAKs and their 7 downstream substrates: the STAT family members. (Ghoreschi *et al.* **2009** *Immunol Rev.* 228(1):273-287.)

[0004] TYK2 is a key component of the JAK-STAT signaling pathway. TYK2 regulates INF α , IL12 and IL23. (Ihle, *et al.* **1995** *Annu Rev Immunol.* 13:369–398; Leonard, *et al.* **1998** *Annu Rev Immunol.* 16:293–322; Liu, *et al.* **1998** *Curr Opin Immunol.* 10:271–278.) Cytokines implicated in TYK2 activation include interferons (*e.g.*, IFN- α , IFN- β , IFN- γ , IFN- δ , IFN- ϵ , IFN- τ , IFN- ω , and IFN- ζ , and interleukins (*e.g.*, IL-4, IL-6, IL-10, IL-11, IL-12, IL-13, IL-22, IL-23, IL-27, IL-31, oncostatin M, ciliary neurotrophic factor, cardiotrophin 1, cardiotrophin-like cytokine, and LIF). The activated TYK2 goes on to phosphorylate further signaling proteins such as members

of the STAT family, including STAT1, STAT2, STAT4, and STAT6. Selective inhibition of TYK2 can be utilized to treat a variety of autoimmune inflammatory diseases, such as psoriasis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), as well as cancer and diabetes.

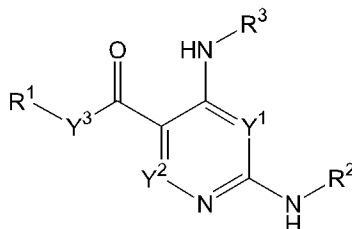
[0005] The selectivity against other JAK family subtypes is regarded as crucial in order to increase the intended pharmacological effects and to reduce side effects. Identifying kinase inhibitors with a high degree of TYK2 selectivity has posed a significant challenge partly due to the high sequence homology of the active site among the JAK family kinases. TYK2 specificity is critical for clinical application of TYK2 kinase inhibitors, because Tyk2 knockout mice are viable with normal blood cell counts, whereas deficiency of JAK3 results in severe combined immunodeficiency in mice, and JAK1 or JAK2 knockout mice show perinatal lethality. (Ghoreschi, *et al.* **2009** *Immunol Rev.* 228:273–287; Karaghiosoff, *et al.* **2000** *Immunity.* 13:549–560; Shimoda, *et al.* **2000** *Immunity.* 13:561–571.) Genetic evidence suggests that pharmacological inhibition of TYK2 should not result in acute toxicity in human patients, but careful monitoring for viral or mycobacterial infections would be warranted in patients treated for prolonged periods. (Akahane, *et al.* **2017** *Br J Haematol.* 177(2): 271–282.)

[0006] An urgent need exists and challenges remain across broad therapeutic areas for selective TYK2 inhibitors with improved potency and minimal side effects.

Summary of the Invention

[0007] The invention provides novel, selective and potent compounds that are orally available. These therapeutic agents are safe and effective TYK2 inhibitors and exhibit fewer and/or lesser side effects than currently available drugs. The invention also provides pharmaceutical compositions of these compounds and methods of their preparation and use.

[0008] In one aspect, the invention generally relates to a compound having the structural formula (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

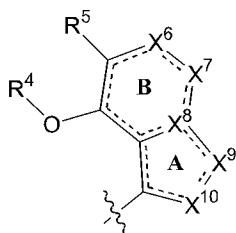
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

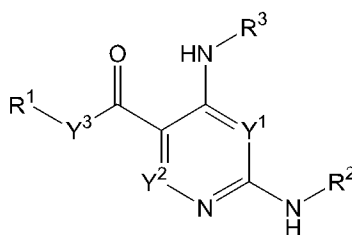
each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 .

[0009] In another aspect, the invention generally relates to a method for preparing a compound disclosed herein, as exemplified by the synthetic schemes and experimental procedure disclosed herein.

[0010] In yet another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein, effective to treat or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0011] In yet another aspect, the invention generally relates to a pharmaceutical composition comprising an amount of a compound having the structural formula of (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof, wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

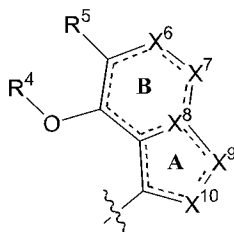
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

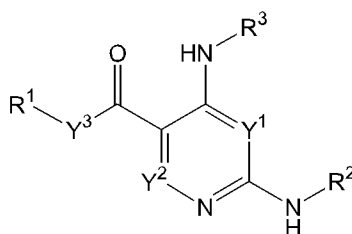
each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 , effective to treat, or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

[0012] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[0013] In yet another aspect, the invention generally relates to a method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-61, wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.

[0014] In yet another aspect, the invention generally relates to a method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the structural formula of (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof, wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

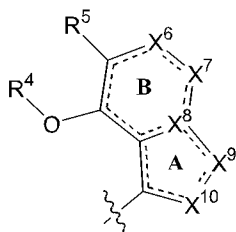
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3 - C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

each of R⁶, R⁷, R⁹ and R¹⁰ is independently selected from H, F, Cl, CN, CD₃, CH₂CF₃, CF₃, OR, NRR', C₁-C₃ alkyl and C₃-C₅ cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a}; and

each of R and R' is independently H or a C₁-C₆ alkyl or acyl, or R and R', together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO₂,

wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.

[0015] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

Definitions

[0016] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. General principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 2006.

[0017] The following terms, unless indicated otherwise according to the context wherein the terms are found, are intended to have the following meanings.

[0018] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 16 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16.

[0019] As used herein, "at least" a specific value is understood to be that value and all values greater than that value.

[0020] As used herein, "more than one" is understood as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 50, 100, etc., or any value therebetween.

[0021] In this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference, unless the context clearly dictates otherwise.

[0022] Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[0023] Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive.

[0024] Any compositions or methods disclosed herein can be combined with one or more of any of the other compositions and methods provided herein.

[0025] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0026] The term “comprising”, when used to define compositions and methods, is intended to mean that the compositions and methods include the recited elements, but do not exclude other elements. The term “consisting essentially of”, when used to define compositions and methods, shall mean that the compositions and methods include the recited elements and exclude other elements of any essential significance to the compositions and methods. For example, “consisting essentially of” refers to administration of the pharmacologically active agents expressly recited and excludes pharmacologically active agents not expressly recited. The term consisting essentially of does not exclude pharmacologically inactive or inert agents, *e.g.*, pharmaceutically acceptable excipients, carriers or diluents. The term “consisting of”, when used to define compositions and methods, shall mean excluding trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0027] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, atropisomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this

invention. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess of either the *R*- or *S*-configuration. For optically active compounds, it is often preferred to use one enantiomer to the substantial exclusion of the other enantiomer.

[0028] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0029] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic methods well known in the art, and subsequent recovery of the pure enantiomers.

[0030] A mixture of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

[0031] Definitions of specific functional groups and chemical terms are described in more detail below. When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0032] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, -C(=O)-O- is equivalent to -O-C(=O)-.

[0033] Structures of compounds of the invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more

of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds that are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions (*e.g.*, aqueous, neutral, and several known physiological conditions).

[0034] Solvates and polymorphs of the compounds of the invention are also contemplated herein. Solvates of the compounds of the present invention include, for example, hydrates.

[0035] As used herein, the term “alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C₁₋₁₀ alkyl). Whenever it appears herein, a numerical range such as “1 to 10” refers to each integer in the given range; *e.g.*, “1 to 10 carbon atoms” means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, “alkyl” can be a C₁₋₆ alkyl group. In some embodiments, alkyl groups have 1 to 10, 1 to 8, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and -n-hexyl; while saturated branched alkyls include, but are not limited to, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)₃, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, -N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tN(R^a)₂ (where t is 1 or 2), -P(=O)(R^a)(R^a), or -O-P(=O)(OR^a)₂ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. In a

non-limiting embodiment, a substituted alkyl can be selected from fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, benzyl, and phenethyl.

[0036] As used herein, the term “alkoxy” refers to the group -O-alkyl, including from 1 to 10 carbon atoms (C_{1-10}) of a straight, branched, saturated cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted alkoxy groups. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy, cyclopropyloxy, cyclohexyloxy and the like. “Lower alkoxy” refers to alkoxy groups containing one to six carbons. In some embodiments, C_{1-3} alkoxy is an alkoxy group that encompasses both straight and branched chain alkyls of from 1 to 3 carbon atoms. Unless stated otherwise in the specification, an alkoxy group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tN(R^a)_2$ (where t is 1 or 2), $-P(=O)(R^a)(R^a)$, or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0037] As used herein, the terms “aromatic” or “aryl” refer to a radical with 6 to 14 ring atoms (*e.g.*, C_{6-14} aromatic or C_{6-14} aryl) that has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted aryl groups. In some embodiments, the aryl is a C_{6-10} aryl group. For example, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in “-yl” by removal of one hydrogen atom from the carbon atom with the free valence are named by adding “-idene” to the name of the

corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 14 aryl" refers to each integer in the given range; *e.g.*, "6 to 14 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, *etc.*, up to and including 14 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In a multi-ring group, only one ring is required to be aromatic, so groups such as indanyl are encompassed by the aryl definition. Non-limiting examples of aryl groups include phenyl, phenalenyl, naphthalenyl, tetrahydronaphthyl, phenanthrenyl, anthracenyl, fluorenyl, indolyl, indanyl, and the like. Unless stated otherwise in the specification, an aryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-\text{Si}(\text{R}^a)_3$, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{OC}(\text{O})-\text{R}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{OR}^a$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{C}(\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{S}(\text{O})_t\text{N}(\text{R}^a)_2$ (where *t* is 1 or 2), $-\text{P}(=\text{O})(\text{R}^a)(\text{R}^a)$, or $-\text{O}-\text{P}(=\text{O})(\text{OR}^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0038] As used herein, the terms "cycloalkyl" and "carbocyclyl" each refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 13 ring atoms (*i.e.*, C_{3-13} cycloalkyl). Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted cycloalkyl groups. Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; *e.g.*, "3 to 13 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, *etc.*, up to and including 13 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused

cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In some embodiments, "cycloalkyl" can be a C₃₋₈ cycloalkyl radical. In some embodiments, "cycloalkyl" can be a C₃₋₅ cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclobutyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆) and the like. Examples of C₃₋₇ carbocyclyl groups include norbornyl (C₇). Examples of C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₇ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C₃₋₁₃ carbocyclyl groups include the aforementioned C₃₋₈ carbocyclyl groups as well as octahydro-1H indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. Unless stated otherwise in the specification, a cycloalkyl group can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, -Si(R^a)₃, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, -N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tN(R^a)₂ (where t is 1 or 2), -P(=O)(R^a)(R^a), or -O-P(=O)(OR^a)₂ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein. The terms "cycloalkenyl" and "cycloalkynyl" mirror the above description of "cycloalkyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein. For example, a cycloalkenyl group can have 3 to 13 ring atoms, such as 5 to 8 ring atoms. In some embodiments, a cycloalkynyl group can have 5 to 13 ring atoms.

[0039] As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I). As used herein, the term "halide" or "halo", means fluoro, chloro, bromo or iodo. The

terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine, such as, but not limited to, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. Each of the alkyl, alkenyl, alkynyl and alkoxy groups are as defined herein and can be optionally further substituted as defined herein.

[0040] As used herein, the term "heteroatom" refers to oxygen (O), nitrogen (N), sulfur (S), and phosphorus (P).

[0041] As used herein, the term "heteroalkyl" refers to an alkyl radical, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted heteroalkyl groups. A numerical range can be given, *e.g.*, C₁₋₄ heteroalkyl, which refers to the chain length in total, which in this example is 4 atoms long. For example, a -CH₂OCH₂CH₃ radical is referred to as a "C₄" heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the parent molecular structure can be through either a heteroatom or a carbon in the heteroalkyl chain. For example, an N-containing heteroalkyl moiety refers to a group in which at least one of the skeletal atoms is a nitrogen atom. One or more heteroatom(s) in the heteroalkyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. For example, heteroalkyl also includes skeletal chains substituted with one or more nitrogen oxide (-O-) substituents. Exemplary heteroalkyl groups include, without limitation, ethers such as methoxyethanyl (-CH₂CH₂OCH₃), ethoxymethanyl (-CH₂OCH₂CH₃), (methoxymethoxy)ethanyl (-CH₂CH₂OCH₂OCH₃), (methoxymethoxy) methanyl (-CH₂OCH₂OCH₃) and (methoxyethoxy)methanyl (-CH₂OCH₂CH₂OCH₃) and the like; amines such as (-CH₂CH₂NHCH₃, -CH₂CH₂N(CH₃)₂, -CH₂NHCH₂CH₃, -CH₂N(CH₂CH₃)(CH₃)) and the like.

[0042] As used herein, the term "heterocycloalkyl" refers to a cycloalkyl radical, which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted heterocycloalkyl

groups. Illustrative examples of heterocycloalkyl include 2-hydroxy-aziridin-1-yl, 3-oxo-1-oxacyclobutan-2-yl, 2,2-dimethyl-tetrahydrofuran-3-yl, 3-carboxy-morpholin-4-yl, 1-cyclopropyl-4-methyl-piperazin-2-yl, 2-pyrrolinyl, 3-pyrrolinyl, dihydro-2H-pyran-2-yl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, etc.

[0043] As used herein, the term “heteroaryl” or, alternatively, “heteroaromatic” refers to a radical of a 5-18 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic, tetracyclic and the like) aromatic ring system (*e.g.*, having 6, 10 or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur (“5-18 membered heteroaryl”). Unless stated otherwise in the specification, the term is intended to include both substituted and unsubstituted heteroaryl groups. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. Whenever it appears herein, a numerical range such as “5 to 18” refers to each integer in the given range; *e.g.*, “5 to 18 ring atoms” means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, *etc.*, up to and including 18 ring atoms. In some instances, a heteroaryl can have 5 to 14 ring atoms. In some embodiments, the heteroaryl has, for example, bivalent radicals derived from univalent heteroaryl radicals whose names end in “-yl” by removal of one hydrogen atom from the atom with the free valence are named by adding “-ene” to the name of the corresponding univalent radical, *e.g.*, a pyridyl group with two points of attachment is a pyridylene.

[0044] For example, an N-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

[0045] “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocycyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl and

the like), the point of attachment to the parent molecular structure can be on either ring, i.e., either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[0046] Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4] oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzopyranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno [2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazoliny, 5,6-dihydrobenzo[h]cinnoliny, 6,7-dihydro-5H benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo [3,2 -c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d] pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10- hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indoliziny, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazoliny, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-

oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo [4,5] thieno [2,3 -d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno [2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno [2,3-c]pyridinyl, and thiophenyl (*i.e.*, thienyl). Unless stated otherwise in the specification, a heteroaryl moiety can be optionally substituted by one or more substituents which independently include: acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-\text{Si}(\text{R}^a)_3$, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{OC}(\text{O})-\text{R}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{OR}^a$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{R}^a$, $-\text{N}(\text{R}^a)\text{C}(\text{O})\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{C}(\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{N}(\text{R}^a)\text{S}(\text{O})_t\text{N}(\text{R}^a)_2$ (where t is 1 or 2), $-\text{P}(=\text{O})(\text{R}^a)(\text{R}^a)$, or $-\text{O}-\text{P}(=\text{O})(\text{OR}^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties can be optionally substituted as defined herein.

[0047] As used herein, the term “administering” refers to oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Suitable routes of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[0048] Administration may be by any suitable route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include,

but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

[0049] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies.

[0050] The compound of the invention can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.*, to reduce metabolic degradation).

[0051] The compositions of the present invention can be delivered transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, *etc.*, suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, gels, for example, water or water/propylene glycol solutions.

[0052] The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, **1995** *J. Biomater Sci. Polym. Ed.* 7:623-645; as biodegradable and injectable gel formulations (see, *e.g.*, Gao **1995** *Pharm. Res.* 12:857-863); or, as microspheres for oral administration (see, *e.g.*, Eyles **1997** *J. Pharm. Pharmacol.* 49:669-674).

[0053] As used herein, the terms "disease," "condition," and "disorder" are used interchangeably herein and refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein.

[0054] As used herein, the term "effective amount" of an active agent refers to an amount

sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the patient.

[0055] As used herein, the terms “inhibition,” “inhibit” and “inhibiting” and the like in reference to a biological target (*e.g.*, TYK2) inhibitor interaction refers to negatively affecting (*e.g.*, decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments, inhibition means negatively affecting (*e.g.* decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments, inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (*e.g.*, an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (*e.g.*, an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0056] As used herein, the terms “isolated” or “purified” refer to a material that is substantially or essentially free from components that normally accompany it in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high-performance liquid chromatography.

[0057] As used herein, the term “modulate” refers to the production, either directly or indirectly, of an increase or a decrease, a stimulation, inhibition, interference, or blockage in a measured activity when compared to a suitable control. A “modulator” of a polypeptide or polynucleotide refers to a substance that affects, for example, increases, decreases, stimulates, inhibits, interferes with, or blocks a measured activity of the polypeptide or polynucleotide, when compared to a suitable control. For example, a “modulator” may bind to and /or activate or inhibit the target with measurable affinity, or directly or indirectly affect the normal regulation of a receptor activity.

[0058] As used herein, a “pharmaceutically acceptable form” of a disclosed compound

includes, but is not limited to, pharmaceutically acceptable salts, esters, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives thereof. In one embodiment, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable salts, esters, prodrugs and isotopically labeled derivatives thereof. In some embodiments, a "pharmaceutically acceptable form" includes, but is not limited to, pharmaceutically acceptable isomers and stereoisomers, prodrugs and isotopically labeled derivatives thereof.

[0059] In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchlorate acid or with organic acids such as acetic 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, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, lactic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0060] The salts can be prepared in situ during the isolation and purification of the disclosed compounds, or separately, such as by reacting the free base or free acid of a parent compound with a suitable base or acid, respectively. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt can be chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0061] In certain embodiments, the pharmaceutically acceptable form is a “solvate” (*e.g.*, a hydrate). As used herein, the term “solvate” refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a “hydrate.” Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or 1 to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term “compound” as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0062] In certain embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term “prodrug” (or “pro-drug”) refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.*, hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (*e.g.*, by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a

biological compartment of interest (*e.g.*, the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

[0063] The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7- 9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[0064] Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism. (See, Bundgard, *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, *The Organic Chemistry of Drug Design and Drug Action*, pp. 352-401, Academic Press, San Diego, Calif., 1992.) Prodrugs commonly known in the art include well-known acid derivatives, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, amides prepared by reaction of the parent acid compound with an amine, basic groups reacted to form an acylated base derivative, *etc.* Other prodrug derivatives may be combined with other features disclosed herein to enhance bioavailability. As such, those of skill in the art will appreciate that certain of the presently disclosed compounds having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds having a carbonate, carbamate, amide or alkyl ester moiety covalently bonded to any of the above substituents disclosed herein.

[0065] Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it can enhance absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0066] As used herein, the term "pharmaceutically acceptable" excipient, carrier, or diluent refers to a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or

portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: 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; polyols, such as glycerin, sorbitol, mannitol and 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; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polypropylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0067] As used herein, the term "subject" refers to any animal (*e.g.*, a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. A subject to which administration is contemplated includes, but is not limited to, humans (*e.g.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or other non-human animals, for example, non-human mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), rodents (*e.g.*, rats and/or mice), etc. In certain embodiments, the non-human animal is a mammal. The non-human animal may be a male or female at any stage of development. A non-human animal may be a transgenic animal. Typically, the terms "subject" and "patient" are used interchangeably herein in reference to a human subject.

[0068] As used herein, the terms "treatment" or "treating" a disease or disorder refers to a method of reducing, delaying or ameliorating such a condition before or after it has occurred. Treatment may be directed at one or more effects or symptoms of a disease and/or the underlying pathology. The treatment can be any reduction and can be, but is not limited to, the complete ablation of the disease or the symptoms of the disease. Treating or treatment thus refers to any

indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, for example, the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. As compared with an equivalent untreated control, such reduction or degree of amelioration may be at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, or 100% as measured by any standard technique.

[0069] Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. The administering step may be a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the patient's age, the concentration of the compound, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

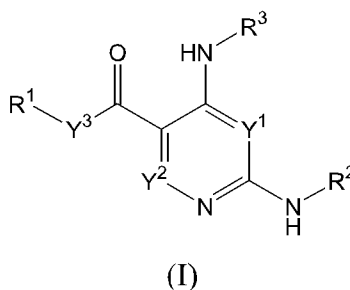
Detailed Description of the Invention

[0070] The invention is based on an unexpected discovery of novel, selective and potent compounds that are TYK2 inhibitors. The invention also provides pharmaceutical compositions of these compounds and methods of their preparation and use. The compounds are orally available and exhibit fewer and/or lesser side effects than currently available drugs.

[0071] The new class of TYK2 inhibitors disclosed herein exhibit exceptional potency profiles and are useful in treating one or more TYK2-mediated diseases and conditions, such as allergic, autoimmune, inflammatory, metabolic, neurological and proliferative diseases and conditions. Without wishing to be bound by the theory, compounds of the invention are modulators of interleukins (*e.g.*, IL-12, IL-23) and interferons (*e.g.*, IFN- α) by inhibiting TYK2-mediated signal transduction.

[0072] These compounds are designed to show good potency against TYK2 with good oral absorption and good *in vivo* stability. The invention also provides pharmaceutical compositions of these compounds and methods of preparation and use thereof. The TYK2 inhibitors disclosed herein exhibit favorable pharmacokinetic profiles and drug properties that are suitable for the target indications.

[0073] In one aspect, the invention generally relates to a compound having the structural formula (I):



or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

Y¹ is CH, CF or N;

Y² is CH or N;

Y³ is NR, O, CH₂, CF₂ or O-NH;

R¹ is a H, F, C₁-C₃ alkyl and CD₃, provided that R¹ is not F when Y³ is N, O or O-NH;

R² is

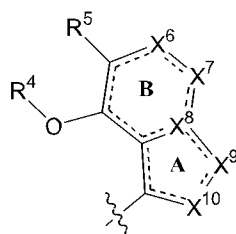
R^{2'}, wherein R^{2'} is a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₅-C₇ spirocycloalkyl, or C₃-C₆ heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a};

(C=O)R^{2b}; or

(C=O)NHR^{2b};

R³ is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 .

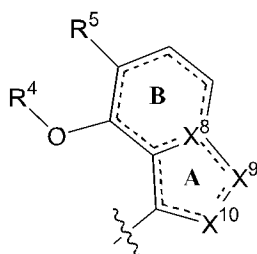
[0074] In certain embodiments, each of Ring A and Ring B is independently a heteroaryl group.

[0075] In certain embodiments, each of Ring A is an aryl group and Ring B is a heteroaryl group.

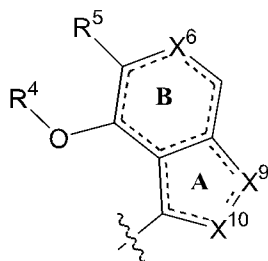
[0076] In certain embodiments, each of Ring A is a heteroaryl group and Ring B is an aryl group.

[0077] In certain embodiments, each of Ring A and Ring B is independently an aryl group.

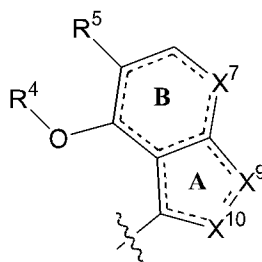
[0078] In certain embodiments, X^6 is CH and X^7 is CH, with R^3 having the structure:



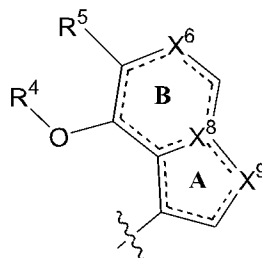
[0079] In certain embodiments, X^7 is CH and X^8 is C, with R^3 having the structure:



[0080] In certain embodiments, X^6 is CH and X^8 is C, with R^3 having the structure:



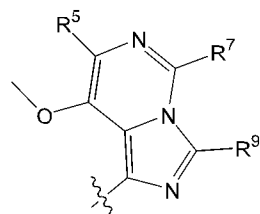
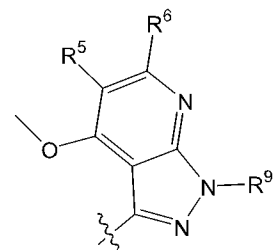
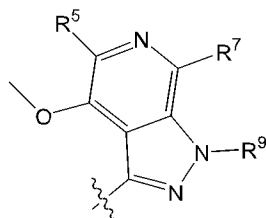
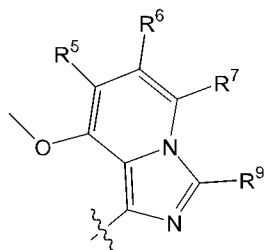
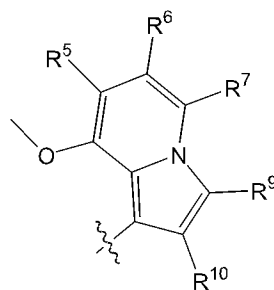
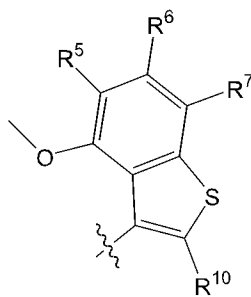
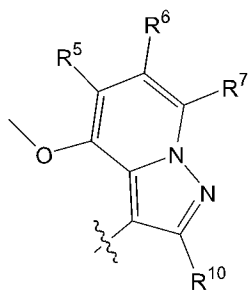
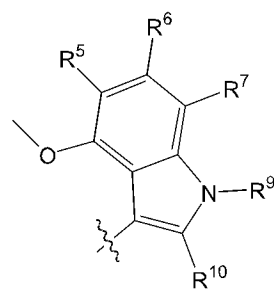
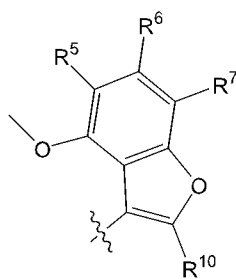
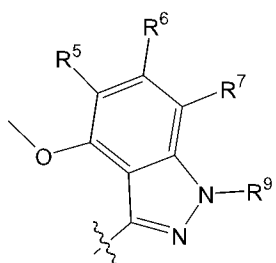
[0081] In certain embodiments, X^7 is CH and X^{10} is CH, with R^3 having the structure:



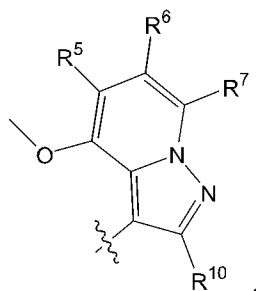
[0082] In certain embodiments, R^4 is CH_3 .

[0083] In certain embodiments, R^4 is CD_3 .

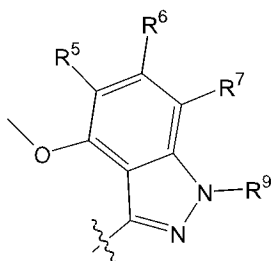
[0084] In certain embodiments, R^3 is selected from:



[0085] In certain embodiments, R^3 is:



[0086] In certain embodiments, R^3 is:



[0087] In certain embodiments, if present R^7 is H.

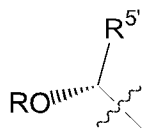
[0088] In certain embodiments, if present R^9 is C_{1-3} alkyl.

[0089] In certain embodiments, if present R^{10} is H.

[0090] In certain embodiments, if present R^{10} is C_{1-3} alkyl.

[0091] In certain embodiments, R^5 is a C_{1-4} alkyl, optionally substituted with an OH, alkoxy or ester group.

[0092] In certain embodiments, R^5 is:



wherein

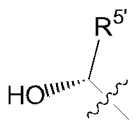
$R^{5'}$ is a C_{1-3} alkyl, substituted with 0-5 F's; and

R is H, C_{1-3} alkyl or acyl.

[0093] In certain embodiments, R is CH_3 .

[0094] In certain embodiments, R is $C(=O)CH_3$.

[0095] In certain embodiments, R is H and R^5 is:

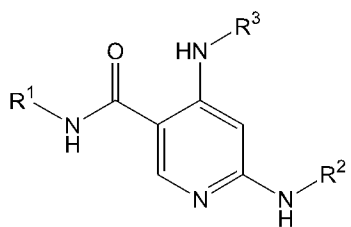


[0096] In certain embodiments, R is CH_3 .

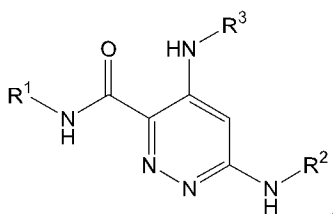
[0097] In certain embodiments, R is $C(=O)CH_3$.

[0098] In certain embodiments, Y^3 is NH.

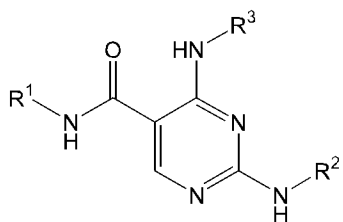
[0099] In certain embodiments, Y^1 is CH and Y^2 is CH:

(I^a)

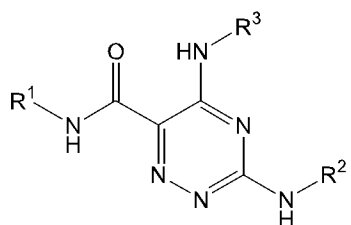
[00100] In certain embodiments, Y¹ is CH and Y² is N:

(I^b)

[00101] In certain embodiments, Y¹ is N and Y² is CH:

(I^c)

[00102] In certain embodiments, Y¹ is N and Y² is N:

(I^d)

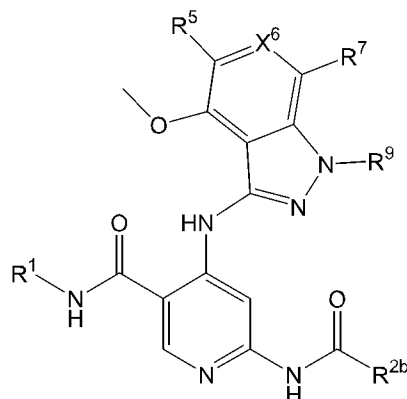
[00103] In certain embodiments, R² is R^{2'}.

[00104] In certain embodiments, R² is (C=O)R^{2b}. In certain embodiments, R^{2b} is selected from C₁-C₆ alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{2c}. In certain embodiments, R^{2b} is cyclopropyl.

[00105] In certain embodiments, R² is (C=O)NHR^{2b}.

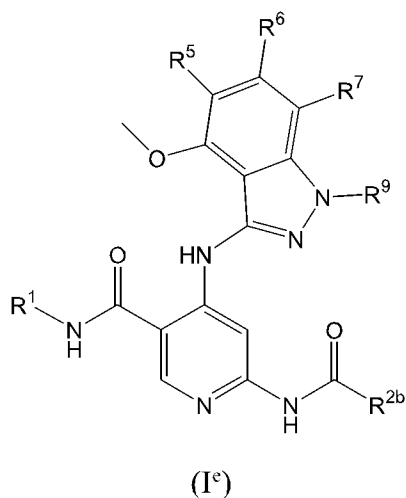
[00106] In certain embodiments, R² is phenyl substituted with 0-2 R^{2b}.

- [00107] In certain embodiments, R^2 is pyridinyl substituted with 0-2 R^{2c} .
- [00108] In certain embodiments, R^2 is pyrazolyl substituted with 0-2 R^{2c} .
- [00109] In certain embodiments, R^2 is pyrimidyl substituted with 0-2 R^{2c} .
- [00110] In certain embodiments, R^1 is CH_3 .
- [00111] In certain embodiments, R^1 is CD_3 .
- [00112] In certain embodiments, the compound of (I) has the structural formula:

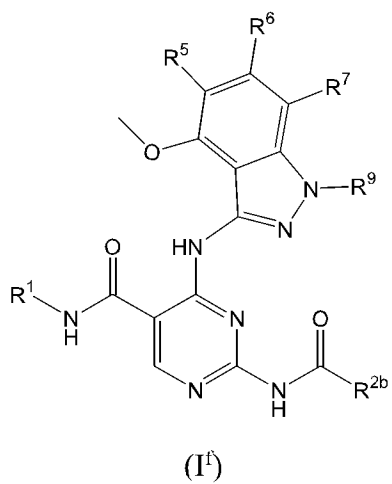


wherein X^6 is N or CH.

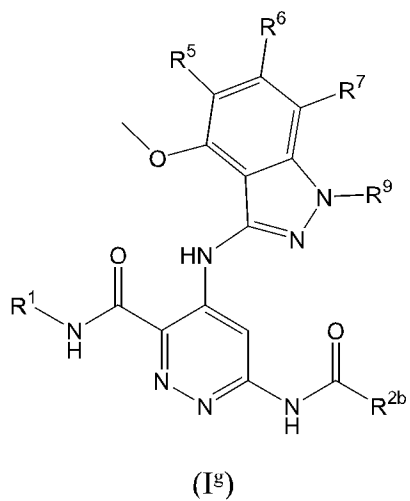
- [00113] In certain embodiments, the compound of (I) has the structural formula:



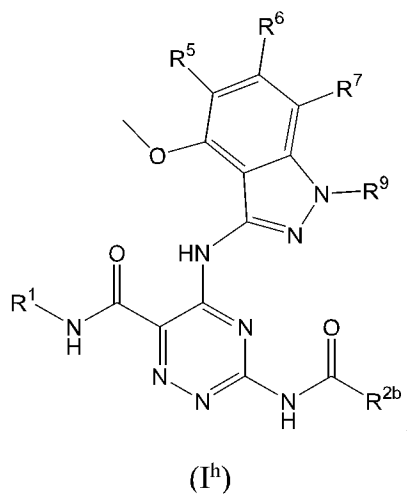
- [00114] In certain embodiments, the compound of (I) has the structural formula:



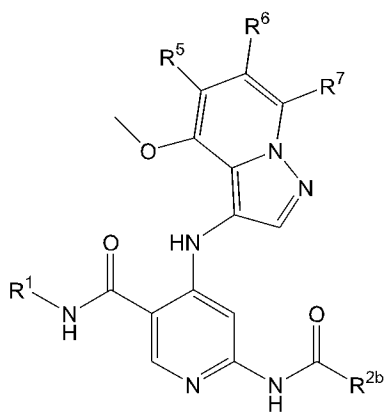
[00115] In certain embodiments, the compound of (I) has the structural formula:



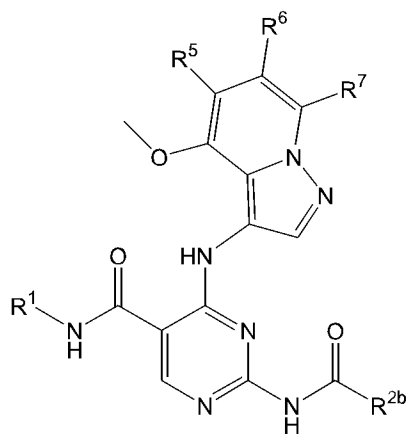
[00116] In certain embodiments, the compound of (I) has the structural formula:



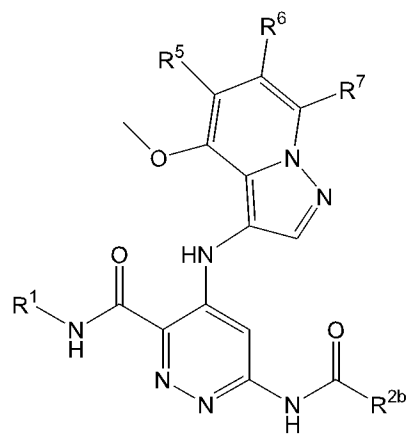
[00117] In certain embodiments, the compound of (I) has the structural formula:

(Iⁱ)

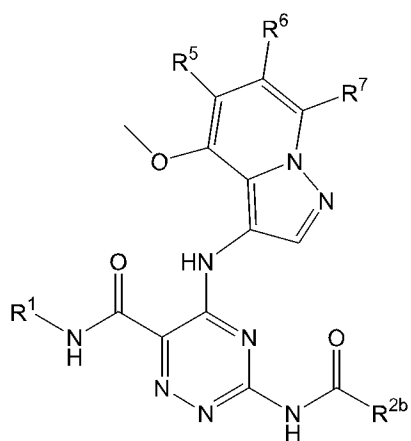
[00118] In certain embodiments, the compound of (I) has the structural formula:

(I^j)

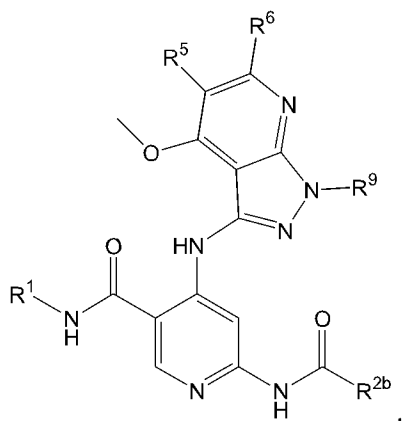
[00119] In certain embodiments, the compound of (I) has the structural formula:

(I^k)

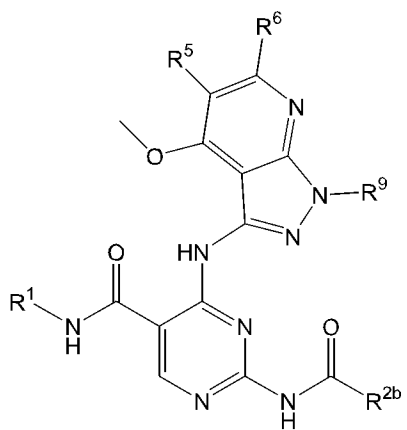
[00120] In certain embodiments, the compound of (I) has the structural formula:

(I^l)

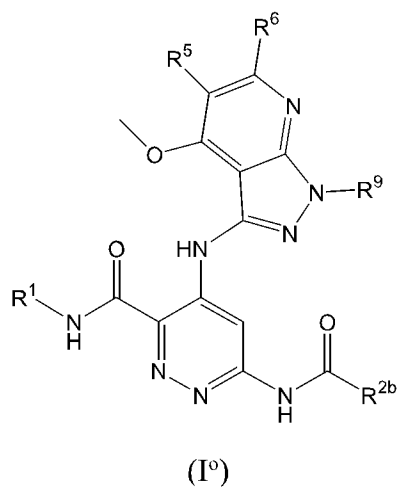
[00121] In certain embodiments, the compound of (I) has the structural formula:

(I^m)

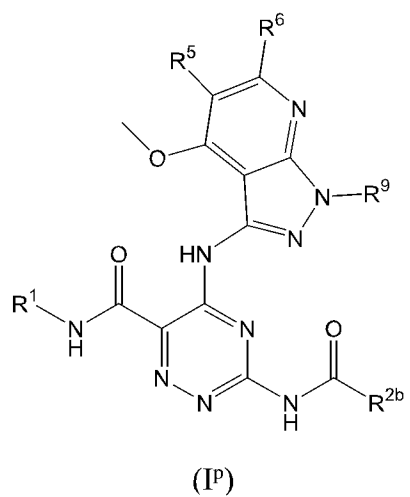
[00122] In certain embodiments, the compound of (I) has the structural formula:

(Iⁿ)

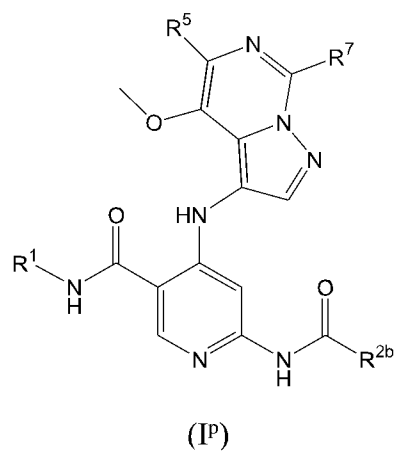
[00123] In certain embodiments, the compound of (I) has the structural formula:



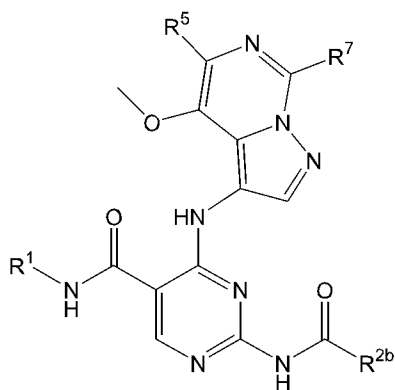
[00124] In certain embodiments, the compound of (I) has the structural formula:



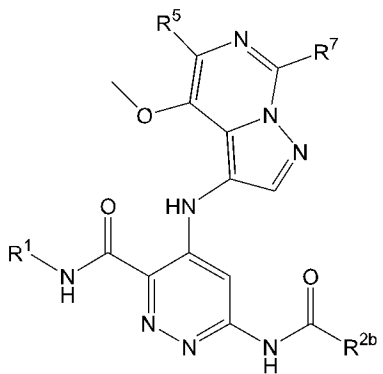
[00125] In certain embodiments, the compound of (I) has the structural formula:



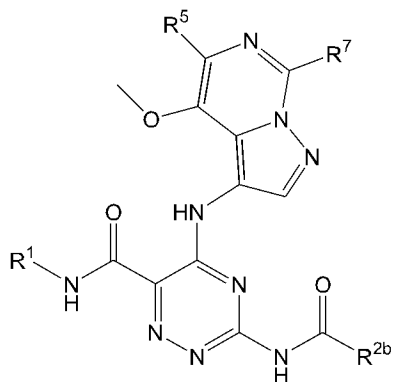
[00126] In certain embodiments, the compound of (I) has the structural formula:

(I^q)

[00127] In certain embodiments, the compound of (I) has the structural formula:

(I^s)

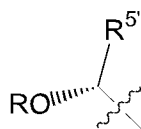
[00128] In certain embodiments, the compound of (I) has the structural formula:

(I^l)

[00129] In certain embodiments of (I)-(I^l), R⁶ and R⁷, if present, each is H.

[00130] In certain embodiments of (I)-(I^l), R^{2b} is C₁-C₆ alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{2c}.

[00131] In certain embodiments of (I)-(I^l), R⁵ is:

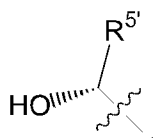


wherein

$R^{5'}$ is a C_{1-3} alkyl, substituted with 0-5 F's; and

R is H, C_{1-3} alkyl or acyl.

[00132] In certain embodiments, R is H and $R^{5'}$ is:



[00133] In certain embodiments, R is CH_3 .

[00134] In certain embodiments, R is $C(=O)CH_3$.

[00135] In certain embodiments of (I)-(I^l), R^1 is CH_3 .

[00136] In certain embodiments of (I)-(I^l), R^1 is CD_3 .

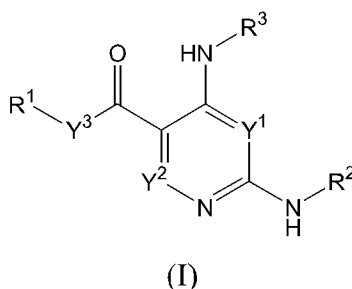
[00137] In certain embodiments of (I)-(I^l), R^1 is CD_3 , R^{2b} is cyclopropyl and $R^{5'}$ is a C_{2-3} alkyl, substituted with 2-5 F's.

[00138] Non-limiting examples of compounds of the invention include those listed in **Table 1** in the Examples section herein.

[00139] In yet another aspect, the invention generally relates to a method for preparing a compound disclosed herein, as exemplified by the synthetic schemes and experimental procedure disclosed herein.

[00140] In another aspect, the invention generally relates to a pharmaceutical composition comprising a compound disclosed herein, effective to treat or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

[00141] In yet another aspect, the invention generally relates to a pharmaceutical composition comprising an amount of a compound having the structural formula of (I):



or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

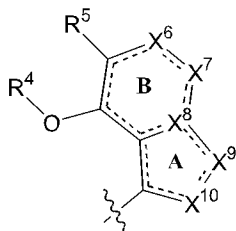
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^{10} , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 , effective to treat, or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

[00142] In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[00143] In certain embodiments, the pharmaceutical composition is suitable for topical administration.

[00144] In certain embodiments, the pharmaceutical composition is suitable for GI-restricted administration.

[00145] In certain embodiments, the pharmaceutical composition is useful to treat or reduce one or more of inflammatory diseases, immune-mediated diseases and cancers, or a related disease or disorder.

[00146] In certain embodiments, the disease or disorder is an inflammatory disease.

[00147] In certain embodiments, the disease or disorder is an immune-mediated disease.

[00148] In certain embodiments, the disease or disorder is cancer.

[00149] In certain embodiments, the disease or disorder is selected from: inflammatory bowel disease, psoriasis, vitiligo, atopic dermatitis, systemic lupus erythematosus, asthma, diabetic nephropathy, chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), breast cancer and ovarian cancer.

[00150] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

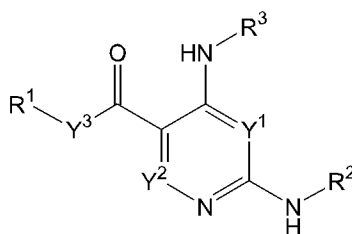
[00151] In certain embodiments, the unit dosage form is a tablet.

[00152] In certain embodiments, the unit dosage form is a capsule.

[00153] In certain embodiments, the unit dosage form is a topical formulation.

[00154] In yet another aspect, the invention generally relates to a method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-61, wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.

[00155] In yet another aspect, the invention generally relates to a method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the structural formula of (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof, wherein

Y¹ is CH, CF or N;

Y² is CH or N;

Y³ is NR, O, CH₂, CF₂ or O-NH;

R¹ is a H, F, C₁-C₃ alkyl and CD₃, provided that R¹ is not F when Y³ is N, O or O-NH;

R² is

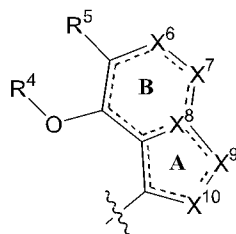
R^{2'}, wherein R^{2'} is a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₅-C₇ spirocycloalkyl, or C₃-C₆ heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a};

(C=O)R^{2b}; or

(C=O)NHR^{2b};

R³ is



wherein

X⁶ is CR⁶ or N;

X⁷ is CR⁷ or N;

X⁸ is C or N;

X⁹ is CR⁹, O, S, N or NR⁹;

X¹⁰ is CR⁹, O, S, N or NR¹⁰; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C₁₋₆ alkyl or C₃₋₆ cycloalkyl, C₅₋₇ spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c};

R^{2c} at each occurrence is independently halo, CN, OR, NRR', OCF₃, CF₃, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a}; and

R⁴ is a C₁₋₃ alkyl, substituted with 0-5 R^{4a}, wherein R^{4a} is selected from D, F and Cl;

R⁵ is H, CN, halo, OCH₃, C(=O)OCH₃, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a}, wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH₃, OCD₃, OCF₃ and OC(=O)CH₃;

each of R⁶, R⁷, R⁹ and R¹⁰ is independently selected from H, F, Cl, CN, CD₃, CH₂CF₃, CF₃, OR, NRR', C₁₋₃ alkyl and C₃₋₅ cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a}; and

each of R and R' is independently H or a C₁₋₆ alkyl or acyl, or R and R', together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO₂,

wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.

[00156] In certain embodiments, the disease or disorder is an inflammatory disease.

[00157] In certain embodiments, the disease or disorder is an immune-mediated disease.

- [00158] In certain embodiments, the disease or disorder is cancer.
- [00159] In certain embodiments, the disease or disorder is selected from: inflammatory bowel disease, psoriasis, vitiligo, atopic dermatitis, systemic lupus erythematosus, asthma, diabetic nephropathy, chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), breast cancer and ovarian cancer.
- [00160] In certain embodiments, administration is via oral administration.
- [00161] In certain embodiments, administration is via topical administration.
- [00162] In certain embodiments, administration is via GI-restricted administration.
- [00163] In yet another aspect, the invention generally relates to use of a compound disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
- [00164] In certain embodiments of the use, the disease or disorder is one or more of inflammatory diseases, immune-mediated diseases and cancer.
- [00165] In certain embodiments of the use, the disease or disorder is an inflammatory disease.
- [00166] In certain embodiments of the use, the disease or disorder is an immune-mediated disease.
- [00167] In certain embodiments of the use, the disease or disorder is cancer.
- [00168] In certain embodiments of the use, the medicament is for oral administration.
- [00169] In certain embodiments of the use, the medicament is for topical administration.
- [00170] In certain embodiments of the use, the medicament is for GI restriction administration.
- [00171] As discussed herein, isotope derivative compounds having one or more hydrogen atoms (*e.g.*, 1, 2, 4, 5, 6, 7, 8, 9, 10, *etc.*) replaced with deuterium atoms are contemplated in the presented invention.
- [00172] The term “inflammatory disease” refers to a disease or condition characterized by aberrant inflammation, *e.g.* an increased level of inflammation compared to a control such as a healthy person not suffering from a disease. Examples of inflammatory diseases that may be treated with a compound, pharmaceutical composition, or method described herein include autoimmune diseases, traumatic brain injury, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), myasthenia gravis, juvenile onset diabetes, diabetes mellitus type 1, Guillain-Barre syndrome, Hashimoto's

encephalitis, Hashimoto's thyroiditis, ankylosing spondylitis, psoriasis, Sjogren's syndrome, vasculitis, glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves ophthalmopathy, inflammatory bowel disease, Addison's disease, Vitiligo, asthma, allergic asthma, acne vulgaris, celiac disease, chronic prostatitis, inflammatory bowel disease, pelvic inflammatory disease, reperfusion injury, ischemia reperfusion injury, stroke, sarcoidosis, transplant rejection, interstitial cystitis, atherosclerosis, scleroderma, and atopic dermatitis. Such conditions are frequently inextricably intertwined with other diseases, disorders and conditions. A non-limiting list of inflammatory-related diseases, disorders and conditions which may, for example, be caused by inflammatory cytokines, include, arthritis, kidney failure, lupus, asthma, psoriasis, colitis, pancreatitis, allergies, fibrosis, surgical complications (*e.g.*, where inflammatory cytokines prevent healing), anemia, and fibromyalgia. Other diseases and disorders, which may be associated with chronic inflammation include Alzheimer's disease, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, osteoporosis, Parkinson's disease, infections, inflammatory bowel disease (IBD), allergic contact dermatitis and other eczemas, systemic sclerosis, transplantation and multiple sclerosis. Some of the aforementioned diseases, disorders and conditions for which a compound of the present disclosure may be particularly efficacious (due to, for example, limitations of current therapies) are described in more detail hereafter.

[00173] The term “autoimmune disease” refers to a disease or condition in which a subject's immune system has an aberrant immune response against a substance that does not normally elicit an immune response in a healthy subject. Examples of autoimmune diseases that may be treated with a compound, pharmaceutical composition, or method described herein include **acne vulgaris**, acute disseminated encephalomyelitis, acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, agammaglobulinemia, **Aicardi-Goutières syndrome (AGS)**, alopecia areata, **alopecia totalis**, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune aplastic anemia, autoimmune dysautonomia, autoimmune hepatitis, autoimmune hyperlipidemia, autoimmune immunodeficiency, autoimmune inner ear disease, autoimmune myocarditis, autoimmune oophoritis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune thrombocytopenic purpura, autoimmune thyroid disease, autoimmune urticaria, axonal or neuronal neuropathies, balo disease, Behcet's disease, bullous pemphigoid, cardiomyopathy,

Castleman disease, celiac disease, Chagas disease, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), chronic active hepatitis, chronic fatigue syndrome, chronic inflammatory demyelinating polyneuropathy, chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogan's syndrome, cold agglutinin disease, congenital heart block, coxsackie myocarditis, CREST disease, Cushing's disease, demyelinating neuropathies, depression, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, dry eye syndrome DES (keratoconjunctivitis sicca), endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, experimental allergic encephalomyelitis, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, graft-versus-host disease (GVDH), Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura, herpes gestationis, hidradenitis suppurativa, hypogammaglobulinemia, idiopathic thrombocytopenic purpura, IgA nephropathy, IgG4-related sclerosing disease, inflammatory bowel disease (IBD), immunoregulatory lipoproteins, inclusion body myositis, interstitial cystitis, juvenile arthritis, juvenile diabetes (Type 1 diabetes), juvenile dermatomyositis (JDM), juvenile myositis, Kawasaki syndrome, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease, lupus, Lyme disease, chronic, Meniere's disease, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis (MS), myasthenia gravis, myositis, narcolepsy, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, pediatric autoimmune neuropsychiatric disorders associated with streptococcus, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria p, Parry Romberg syndrome, Parsonage-Turner syndrome, Pars planitis (peripheral uveitis), pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polycystic ovary syndrome (PCOS), Type I, II, & III autoimmune polyglandular syndromes, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, progesterone dermatitis, primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, plaque psoriasis, idiopathic

pulmonary fibrosis, pyoderma gangrenosum, pure red cell aplasia, Raynauds phenomenon, reactive Arthritis, reflex sympathetic dystrophy, Reiter's syndrome, relapsing polychondritis, restless legs syndrome, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjogren's syndrome, sperm & testicular autoimmunity, stiff person syndrome, stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy (SAVI), subacute bacterial endocarditis, Susac's syndrome, sympathetic ophthalmia, **systemic lupus erythematosus (SLE)**, Takayasu's arteritis, temporal arteritis/Giant cell arteritis, thrombocytopenic purpura, Tolosa-Hunt syndrome, **transplant rejection (allograft transplant rejection)**, transverse myelitis, Type 1 diabetes, ulcerative colitis, undifferentiated connective tissue disease, uveitis, vasculitis, vesiculobullous dermatosis, vitiligo, or Wegener's granulomatosis.

[00174] The term “immune-mediated disease” refers to chronic inflammatory diseases perpetuated by antibodies and cellular immunity. Immune-mediated diseases include, for example, but not limited to, asthma, allergies, arthritis (*e.g.*, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis), juvenile arthritis, inflammatory bowel diseases (*e.g.*, ulcerative colitis and Crohn's disease), endocrinopathies (*e.g.*, type 1 diabetes and Graves' disease), neurodegenerative diseases (*e.g.*, multiple sclerosis (MS)), autistic spectrum disorder, **depression**, Alzheimer's disease, Guillain-Barre syndrome, obsessive-compulsive disorder, optic neuritis, retinal degeneration, **dry eye syndrome DES**, Sjogren's syndrome, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Huntington's Disease, Guillain-Barre syndrome, myasthenia gravis, and chronic idiopathic demyelinating disease (CID)), vascular diseases (*e.g.*, autoimmune hearing loss, systemic vasculitis, and atherosclerosis), and skin diseases (*e.g.*, **acne vulgaris** dermatomyositis, pemphigus, systemic lupus erythematosus (SLE), discoid lupus erythematosus, scleroderma, psoriasis, plaque psoriasis, vasculitics, vitiligo and alopecias). Hashimoto's thyroiditis, pernicious anemia, Cushing's disease, Addison's disease, chronic active hepatitis, polycystic ovary syndrome (PCOS), celiac disease, pemphigus, transplant rejection (allograft transplant rejection), graft-versus-host disease (GVHD).

[00175] The term “cancer” as used herein refers to all types of cancer, neoplasm or malignant tumors found in mammals, *e.g.*, humans, including hematological cancers leukemia, and lymphomas, T-ALL, large B-cell lymphoma, solid cancers such as carcinomas and sarcomas. Exemplary cancers include blood cancer, brain cancer, glioma, glioblastoma, neuroblastoma,

prostate cancer, colorectal cancer, pancreatic cancer, cervical cancer, gastric cancer, ovarian cancer, lung cancer, and cancer of the head. Exemplary cancers include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include penile, skin – non-melanoma, anal, hepatobiliary, esophagogastric, uterine sarcoma, gastrointestinal stromal tumor, salivary gland, peripheral nervous system, soft tissue sarcoma, bone, renal, myeloproliferative neoplasms, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, metastatic leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, round cell liposarcoma or prostate cancer.

[00176] In certain embodiments of the use, the disease or disorder is selected from: inflammatory bowel disease, psoriasis, vitiligo, atopic dermatitis, systemic lupus erythematosus, asthma, diabetic nephropathy, chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), breast cancer and ovarian cancer.

[00177] Isotopically-labeled compounds are also within the scope of the present disclosure. As used herein, an "isotopically-labeled compound" refers to a presently disclosed compound including pharmaceutical salts and prodrugs thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds presently disclosed include isotopes of hydrogen, carbon, nitrogen,

oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

[00178] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^3H) and carbon-14 (^{14}C) labeled compounds are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds presently disclosed, including pharmaceutical salts, esters, and prodrugs thereof, can be prepared by any means known in the art.

[00179] Further, substitution of normally abundant hydrogen (^1H) with heavier isotopes such as deuterium can afford certain therapeutic advantages, *e.g.*, resulting from improved absorption, distribution, metabolism and/or excretion (ADME) properties, creating drugs with improved efficacy, safety, and/or tolerability. Benefits may also be obtained from replacement of normally abundant ^{12}C with ^{13}C . (See, WO 2007/005643, WO 2007/005644, WO 2007/016361, and WO 2007/016431.)

[00180] Stereoisomers (*e.g.*, cis and trans isomers) and all optical isomers of a presently disclosed compound (*e.g.*, R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers are within the scope of the present disclosure.

[00181] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 95% ("substantially pure"), which is then used or formulated as described herein. In certain embodiments, the compounds of the present invention are more than 99% pure.

Solvates and polymorphs of the compounds of the invention are also contemplated herein.

Solvates of the compounds of the present invention include, for example, hydrates.

[00182] Any appropriate route of administration can be employed, for example, parenteral, intravenous, subcutaneous, intramuscular, intraventricular, intracorporeal, intraperitoneal, rectal, or oral administration. Most suitable means of administration for a particular patient will depend on the nature and severity of the disease or condition being treated or the nature of the therapy being used and on the nature of the active compound.

[00183] Solid dosage forms for oral administration include capsules, tablets, pills, powders,

and granules. In such solid dosage forms, the compounds described herein or derivatives thereof are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (i) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (ii) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (iii) humectants, as for example, glycerol, (iv) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (v) solution retarders, as for example, paraffin, (vi) absorption accelerators, as for example, quaternary ammonium compounds, (vii) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (viii) adsorbents, as for example, kaolin and bentonite, and (ix) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. 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 polyethyleneglycols, and the like. Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others known in the art.

[00184] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, 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 water or other solvents, solubilizing agents, and emulsifiers, such as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan, or mixtures of these substances, and the like. Besides such inert diluents, the composition can also include additional agents, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

[00185] Materials, compositions, and components disclosed herein can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. It is understood that when combinations, subsets, interactions, groups, *etc.* of these materials are disclosed that while specific reference of each various individual and

collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including in the method are discussed, each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

[00186] The following examples are meant to be illustrative of the practice of the invention and not limiting in any way.

Examples

Abbreviations

Methanol:	MeOH
Dichloromethane:	DCM
Petroleum ether:	PE
Ethyl acetate:	EtOAc or EA
Acetonitrile:	ACN or MeCN
Isopropanol:	IPA
Triethylamine:	TEA
Sodium hydroxide:	NaOH
Propylphosphonic Acid Anhydride:	T ₃ P
Nitrogen:	N ₂
<i>N,N</i> -Diisopropylethylamine:	DIPEA
<i>N,N</i> -Dimethylformamide:	DMF
4-Methylbenzenesulfonic acid:	pTSA or TsOH

Diphenyl phosphorazidate:	DPPA
N-Iodosuccinimide:	NIS
Tetrabutylammonium fluoride:	TBAF
Methanesulfonyl chloride:	MsCl
Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate:	MDFA
Tosylmethyl isocyanide:	TosMIC
Diethylaminosulphur trifluoride:	DAST
Thin-Layer Chromatography:	TLC
High Performance Liquid Chromatography:	HPLC
Room temperature:	r.t.
Hours:	h
Diethylamine:	DEA

[00187] Representative methods of *prep*-HPLC: Flow rate and gradient may change.

[00188] Exemplary methods for *prep*-HPLC are provided below.

[00189] Method A: NH₄HCO₃: Column: Gilson2-Xbridge C18 19*150 mm, 5 μm; mobile phase: CH₃CN in water (0.1% NH₄HCO₃) from 20% to 60%, Flow rate: 15 mL/min.

[00190] Method B: TFA: Column: Waters-Xbridge C18 10*190 mm, 5 μm; mobile phase: CH₃CN in water (0.1% TFA) from 15% to 40%, Flow rate: 15 mL/min.

[00191] Method C: HCOOH: Column: Waters-Xbridge C18 10*190 mm, 5 μm; mobile phase: CH₃CN in water (0.1% formic acid) from 15% to 40%, Flow rate: 15 mL/min.

[00192] Method D: HCOOH: Column: Waters SunFire® Prep C18 OBDTM (5 micron, 19*150 mm); mobile phase: CH₃CN in water (0.1% formic acid) from 18% to 38%, Flow rate: 20 mL/min.

[00193] Method E: NH₄HCO₃: Column: Waters Xbridge® Prep C18 OBD™ (5 micron, 19*150 mm); mobile phase: CH₃CN in water (10 mM NH₄HCO₃) from 20% to 60%, Flow rate: 20 mL/min.

Representative method of chiral *prep*-HPLC:

[00194] Method F: Gilson 281, Daicel Chiralpak IE, 10 μm, 30*250 mm; Mobile phase:

Hexane/EtOH/Diethylamine = 70/30/0.3, Flow rate: 25 mL/min.

[00195] Method G: Gilson 281, Daicel Chiralpak IG, 10 μ m, 30*250 mm; Mobile phase: Hexane/EtOH = 70/30, Flow rate: 25 mL/min.

[00196] Method H: Gilson 281, Daicel Chiralpak IB N, 10 μ m, 30*250 mm; Mobile phase: Hexane/IPA/Diethylamine = 80/20/0.3, Flow rate: 30 mL/min.

[00197] Method I: Gilson 281, Daicel Chiralpak IA, 10 μ m, 30*250 mm; Mobile phase: Hexane/EtOH/Diethylamine = 30/70/0.3, Flow rate: 25 mL/min.

Representative methods of analytical-HPLC

[00198] Method 1: Analysis was performed on an Agilent 1200_series HPLC-6120MS. UHPLC Long Gradient Equivalent 5% to 95% acetonitrile in water (containing 0.02% NH₄OAc) run time of 6.5 minutes with a flow rate of 1.5 mL/min. A Waters Xbridge C18 column (18.5 micron, 4.6*50 mm) was used at a temperature of 40 °C.

[00199] Method 2: Analysis was performed on an Agilent 1200_series HPLC-6120MS. UHPLC Long Gradient Equivalent 5% to 95% acetonitrile in water (containing 0.1% trifluoroacetic acid) run time of 6.5 minutes with a flow rate of 1.5 mL/min. A Waters Xbridge C18 column (18.5 micron, 4.6*50 mm) was used at a temperature of 40 °C.

[00200] Method 3: Analysis was performed on an Agilent 1260_series HPLC-6120MS. UHPLC Long Gradient Equivalent 5% to 95% acetonitrile in water (containing 0.02% NH₄OAc) run time of 2.5 minutes with a flow rate of 0.5 mL/min. A Diamonsil Plus C18 column (18.5 micron, 4.6*30 mm) was used at a temperature of 40 °C.

[00201] Method 4: Analysis was performed on an Agilent 1260_series HPLC-6125C MS. HPLC Long Gradient Equivalent 20% to 100% acetonitrile in water (containing 0.1% FA) run time of 6 minutes with a flow rate of 0.8 mL/min. Agilent ZORBAX SB-C18 column (1.8 micron, 2.1*50 mm) was used at a temperature of 30 °C.

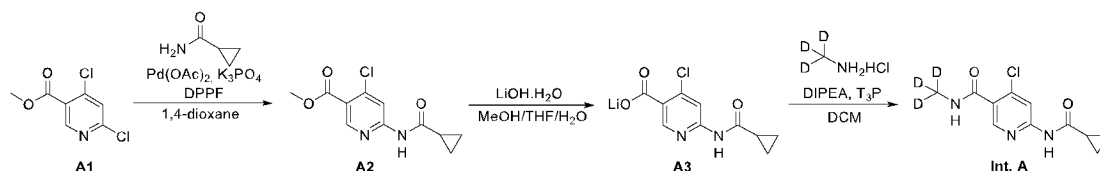
[00202] Method 5: Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/EtOH/DEA (70/30/0.2) run time of 20 minutes with a flow rate of 1 mL/min. CHIRALPAK IE (5 μ m, 4.6*250 mm) was used at a temperature of 30 °C.

[00203] Method 6: Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/EtOH/DEA (30/70/0.2) run time of 30 minutes with a flow rate of 1 mL/min. CHIRALPAK IA (5 μ m, 4.6*250 mm) was used at a temperature of 30 °C.

[00204] **Method 7:** Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/IPA/DEA (80/20/0.2) run time of 30 minutes with a flow rate of 1 mL/min. CHIRALPAK IB N-5 (5 μ m, 4.6*250 mm) was used at a temperature of 30 °C.

[00205] **Method 8:** Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/EtOH (70/30) run time of 30 minutes with a flow rate of 1 mL/min. CHIRALPAK IG (5 μ m, 4.6*250 mm) was used at a temperature of 30 °C.

Intermediate A



Step 1. Methyl 4-chloro-6-(cyclopropanecarboxamido) nicotinate (**A2**)

[00206] A mixture of **A1** (2.0 g, 9.71 mmol), cyclopropanecarboxamide (826 mg, 9.71 mmol), $\text{Pd}(\text{OAc})_2$ (109 mg, 0.49 mmol), dppf (538 mg, 0.97 mmol), K_3PO_4 (4.12 g, 19.42 mmol) in dioxane (30 mL) was stirred at 90 °C for 4 h under N_2 . The mixture was diluted with H_2O (100 mL), extracted with EtOAc (30 mL*3), washed with brine (30 mL), dried over Na_2SO_4 , concentrated and purified by flash chromatography (PE/EA = 10/1 to 1/1) to get compound **A2** (1.8 g, 73% yield) as a white solid. LC-MS (ESI, Method 4) t_{R} = 3.33 min, m/z ($\text{M}+\text{H}$)⁺ = 255.0.

Step 2. Lithium 4-chloro-6-(cyclopropanecarboxamido)nicotinate (**A3**)

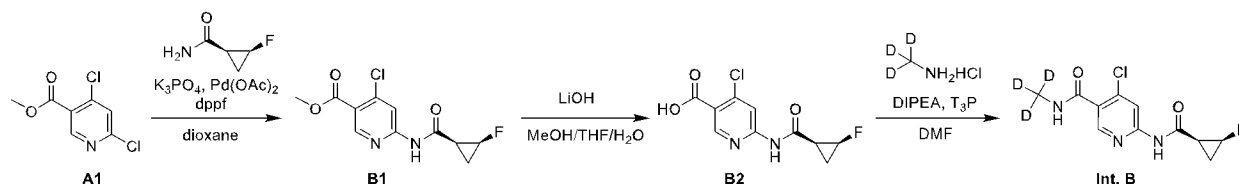
[00207] To a solution of **A2** (500 mg, 1.96 mmol) in a co-solvent of MeOH (2 mL), THF (2 mL) and water (1 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (165 mg, 3.93 mmol). Then the mixture was stirred at r.t. overnight. The mixture was concentrated to dryness to give compound **A3** (480 mg, 99% yield) as a white solid. LC-MS (ESI, Method 4) t_{R} = 3.81 min, m/z ($\text{M}+\text{H}$)⁺ = 241.1.

Step 3. 4-Chloro-6-(cyclopropanecarboxamido)- N -(methan- d_3)nicotinamide (**Int. A**)

[00208] To a solution of **A3** (480 mg, 1.95 mmol) in DCM (15 mL) was sequentially added methan- d_3 -amine hydrochloride (275 mg, 3.89 mmol), DIPEA (1.51 g, 11.68 mmol) and T_3P (1.86 g, 2.92 mmol, 50% in EtOAc) at 0 °C. The resulting mixture was stirred at r.t. overnight. The mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL*3). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was

concentrated to dryness to give **Int. A** (300 mg, 60% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 2.25$ min, m/z ($M+H$)⁺ = 257.1.

Intermediate B



Step 1. Methyl 4-chloro-6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)nicotinate (**B1**)

[00209] A mixture of **A1** (1.0 g, 4.85 mmol), (1*S*,2*S*)-2-fluorocyclopropane-1-carboxamide (751 mg, 7.28 mmol), K_3PO_4 (2.04 g, 9.67 mmol), dppf (269 mg, 0.49 mmol) and $Pd(OAc)_2$ (109 mg, 0.49 mmol) in dioxane (8 mL) was stirred at 90 °C for 12 h under N_2 . After cooling to r.t., the mixture was filtered and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 30/1) to afford **B1** (220 mg, 17% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.16$ min, m/z ($M+H$)⁺ = 273.6.

Step 2. 4-Chloro-6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)nicotinic acid (**B2**)

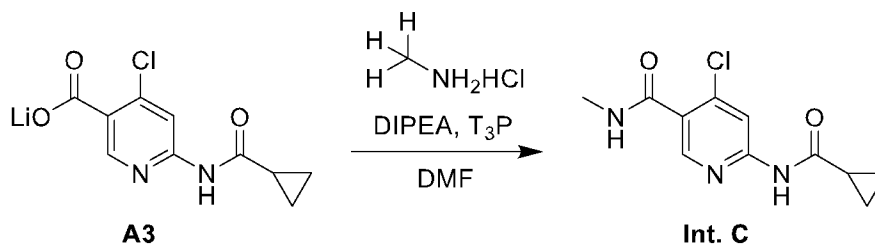
[00210] To a solution of **B1** (900 mg, 3.30 mmol) in MeOH/THF/ H_2O (15 mL, v/v/v = 2/2/1) was added $LiOH \cdot 2H_2O$ (990 mg, 16.50 mmol) and stirred at 25 °C for 12 h. The reaction mixture was concentrated to dryness and acidified with 1 *N* HCl to pH = 2. The formed solid was filtered and the filter cake was dried to afford **B2** (700 mg, 82% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.00$ min, m/z ($M+H$)⁺ = 258.9.

Step 3. 4-Chloro-6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-*N*-(methan-*d*₃)nicotinamide (**Int. B**)

[00211] A mixture of **B2** (700 mg, 2.71 mmol), DIPEA (2.10 g, 16.24 mmol, 2.83 mL), T_3P (1.72 g, 5.41 mmol, 3.45 mL, 50% wt. in DMF) and methan-*d*₃-amine hydrochloride (379 mg, 5.41 mmol) in DMF (4 mL) was stirred at 30 °C for 48 h. The mixture was diluted with H_2O (10 mL), extracted with DCM (10*3 mL). The organic layer was washed with brine (2 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford **Int. B** (500 mg, 67% yield) as a white solid. ^1H NMR (400 MHz, $DMSO-d_6$) δ 11.24 (s, 1H), 8.43 (s, 1H), 8.29 (s, 1H), 8.19 (s, 1H), 5.04-4.86 (m,

1H), 2.49-2.40 (m, 1H), 1.69-1.62 (m, 1H), 1.24-1.18 (m, 1H). LC-MS (ESI, Method 3) t_R = 0.91 min, m/z ($M+H$)⁺ = 275.0.

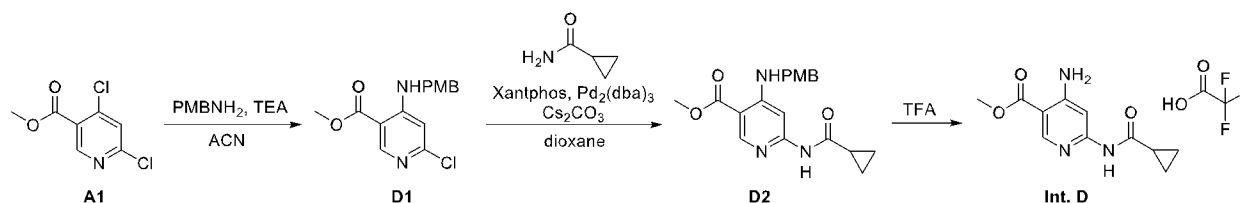
Intermediate C



Step 1. 4-Chloro-6-(cyclopropanecarboxamido)-N-methylnicotinamide (Int. C)

[00212] A mixture of **A3** (338 mg, 1.37 mmol), DIPEA (1.06 g, 8.23 mmol), methylamine hydrochloride (184 mg, 2.75 mmol) and T₃P (1.75 g, 2.74 mmol, 50% wt. in DMF) in DMF (2 mL) was stirred at 50 °C for 24 h. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (20 mL*3). The separated organic layer was washed with water (5 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to afford **Int. C** (120 mg, 34% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.19 (s, 1H), 8.46 (s, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 2.75 (d, J = 5.2 Hz, 3H), 2.02-1.99 (m, 1H), 0.85-0.82 (m, 4H). LC-MS (ESI, Method 3) t_R = 0.94 min, m/z ($M+H$)⁺ = 254.2.

Intermediate D



Step 1. Methyl 6-chloro-4-((4-methoxybenzyl)amino)nicotinate (D1)

[00213] To a solution of **A1** (5 g, 24.27 mmol) in ACN (8 mL) was added (4-methoxyphenyl)methanamine (3.33 g, 24.27 mmol, 3.2 mL) and TEA (4.91 g, 48.54 mmol, 6.8 mL). Then the mixture was stirred at r.t. for 24 h. The mixture was diluted with H₂O (100 mL), extracted with EA (50 mL*3), washed with brine, dried over Na₂SO₄, concentrated and purified by flash chromatography (PE/EA = 20/1 to 5/1) to get compound **D1** (6.5 g, 87% yield) as an off-

white solid. LC-MS (ESI, Method 4) $t_R = 4.18$ min, m/z (M+H)⁺ = 307.1.

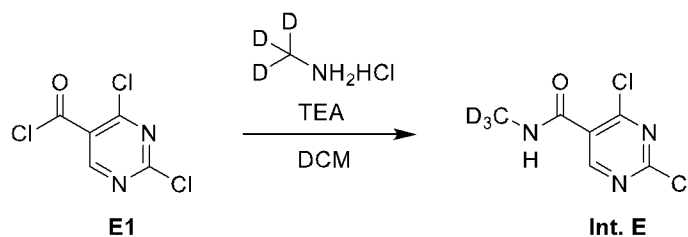
Step 2. Methyl 6-(cyclopropanecarboxamido)-4-((4-methoxybenzyl)amino) nicotinate (D2)

[00214] A mixture of **D1** (2 g, 6.52 mmol), cyclopropanecarboxamide (1.11 g, 13.04 mmol), XantPhos (754 mg, 1.30 mmol), Pd₂(dba)₃ (597 mg, 0.65 mmol), Cs₂CO₃ (5.31 g, 16.30 mmol) in 1,4-dioxane (30 mL) was stirred at 110 °C for 2 h. Then the mixture was diluted with H₂O (100 mL), extracted with EA (60 mL*3), washed with brine, dried over Na₂SO₄ and concentrated to get compound **D2** (2.3 g, 99% yield) as a yellow solid. LC-MS (ESI, Method4) $t_R = 2.91$ min, m/z (M+H)⁺ = 356.2.

Step 3. Methyl 4-amino-6-(cyclopropanecarboxamido)nicotinate 2,2,2-trifluoroacetate (Int. D)

[00215] A solution of **D2** (2.1 g, 5.91 mmol) in TFA (10 mL) was stirred at 80 °C for 16 h. Then the mixture was concentrated and diluted with EA (10 mL), filtered and wash with EA (5 mL*2). Then the solid was dried to get compound **Int. D** (1.8 g, 87% yield, TFA salt) as an off-white solid. LC-MS (ESI, Method 4) $t_R = 1.28$ min, m/z (M+H)⁺ = 236.2.

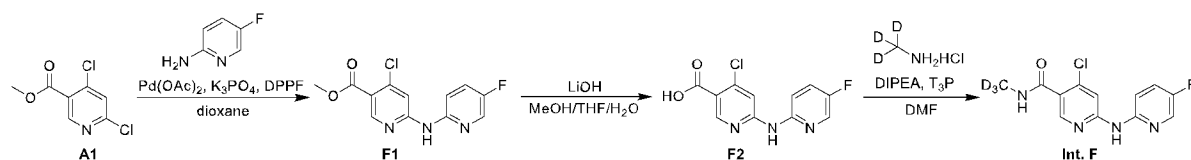
Intermediate E



Step 1. 2,4-Dichloro-N-(methyl-*d*₃)pyrimidine-5-carboxamide (Int. E)

[00216] To a mixture of methan-*d*₃-amine hydrochloride (1.40 g, 19.86 mmol) in DCM (200 mL) was added **E1** (3.5 g, 16.55 mmol) slowly followed by TEA (1.68 g, 16.55 mmol, 2.31 mL) at -78 °C. After stirring for 1 h at this temperature, the reaction was quenched with water (30 mL). The organic layer was separated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to afford **Int. E** (1.38 g, 35% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (s, 1H), 8.85 (s, 1H). LC-MS (ESI, Method 3) $t_R = 0.80$ min, m/z (M+H)⁺ = 208.9.

Intermediate F



Step 1. Methyl 4-chloro-6-((5-fluoropyridin-2-yl)amino)nicotinate (F1)

[00217] A mixture of **A1** (2.0 g, 9.71 mmol), 5-fluoropyridin-2-amine (1.31 g, 11.65 mmol), K_3PO_4 (4.12 g, 19.42 mmol), DPPF (807 mg, 1.46 mmol) and $Pd(OAc)_2$ (327 mg, 1.46 mmol) in anhydrous dioxane (20 mL) was stirred at 90 °C for 12 h. After cooling to r.t., the mixture was filtered and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 7/1) to afford **F1** (2.0 g, 73% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.11 min, m/z ($M+H$)⁺ = 282.4.

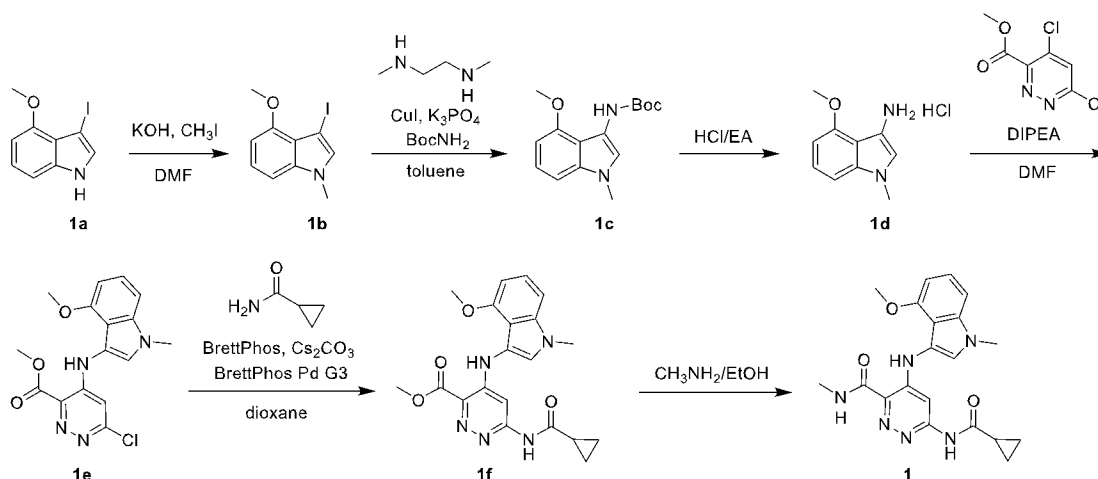
Step 2. 4-Chloro-6-((5-fluoropyridin-2-yl)amino)nicotinic acid (F2)

[00218] To a solution of **F1** (2.0 g, 7.10 mmol) in MeOH/THF/H₂O (20 mL, v/v/v = 2/2/1) was added LiOH.H₂O (1.49 g, 35.50 mmol). After stirring at r.t. for 12 h, the reaction mixture was concentrated to dryness and acidified with 1 N HCl to pH = 2. The formed solid was collected by filtering and the filter cake was dried to give compound **F2** (1.8 g, 95% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 0.88 min, m/z ($M+H$)⁺ = 268.2.

Step 3. 4-Chloro-6-((5-fluoropyridin-2-yl)amino)-N-(methyl-*d*₃)nicotinamide (Int. F)

[00219] A mixture of **F2** (400 mg, 1.50 mmol), methan-*d*₃-amine hydrochloride (529 mg, 7.50 mmol) and DIPEA (1.16 g, 9.00 mmol) in T₃P (2 mL, 50% wt in DMF) was stirred at 50 °C for 16 h. After cooling to r.t., the reaction mixture was poured into water (10 mL) and the formed solid was collected by filtering. The filter cake was slurried with MeOH (5 mL) for 30 min. The solid was filtered and dried to afford **Int. F** (380 mg, 90% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.10 min, m/z ($M+H$)⁺ = 284.1.

Example 1



Step 1. 3-Iodo-4-methoxy-1-methyl-1H-indole (1b)

[00220] To a solution of **1a** (2.78 g, 10.18 mmol) in DMF (15 mL) was added KOH (2.28 g, 40.72 mmol) and CH₃I (4.34 g, 30.54 mmol) at 0 °C. The mixture was stirred at r.t. for 1 h. The reaction mixture was poured into ice-water (50 mL) and the formed solid was filtered. The solid was dried to give compound **1b** (2.8 g, 96% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.37 (s, 1H), 7.11-7.05 (m, 2H), 6.55 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H).

Step 2. *Tert*-butyl (4-methoxy-1-methyl-1H-indol-3-yl)carbamate (1c)

[00221] A mixture of **1b** (500 mg, 1.74 mmol), K₃PO₄ (738 mg, 3.48 mmol), BocNH₂ (612 mg, 5.22 mmol), CuI (100 mg, 0.52 mmol) and *N,N*-dimethylethane-1,2-diamine (46 mg, 0.52 mmol) in toluene (5 mL) was stirred at 110 °C overnight. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to give compound **1c** (240 mg, 50% yield) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.76 (s, 1H), 7.34 (s, 1H), 7.10-6.97 (m, 2H), 6.52 (d, *J* = 10.4 Hz, 1H), 3.90 (s, 3H), 3.71 (s, 3H), 1.50 (s, 9H).

Step 3. 4-Methoxy-1-methyl-1H-indol-3-amine hydrochloride (1d)

[00222] To a solution of **1c** (300 mg, 1.09 mmol) in EtOAc (2 mL) was added HCl/EA (2 mL, 6 M) at r.t. The mixture was stirred at r.t. overnight. The formed solid was filtered and the filter cake was dried to give compound **1d** (158 mg, 68% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (brs, 3H), 7.37 (s, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.64

(d, $J = 8.0$ Hz, 1H), 3.94 (s, 3H), 3.76 (s, 3H).

Step 4. Methyl 6-chloro-4-((4-methoxy-1-methyl-1*H*-indol-3-yl)amino)pyridazine-3-carboxylate (1e)

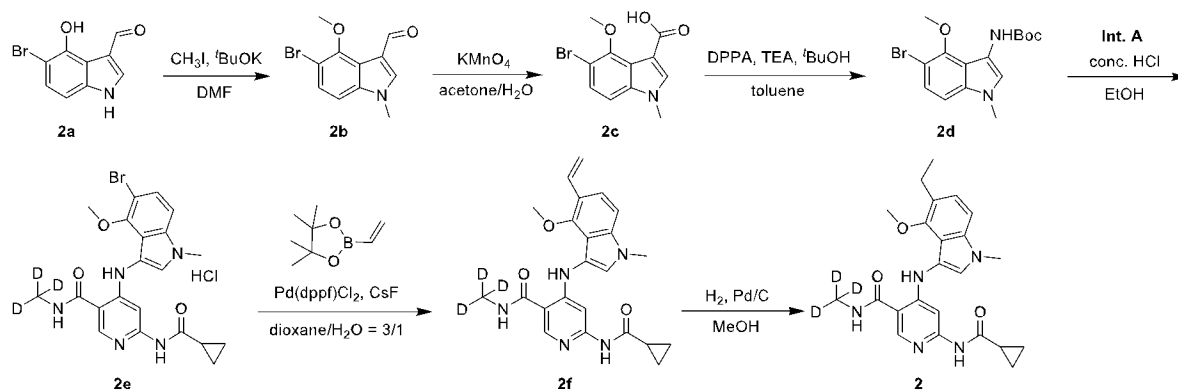
[00223] A mixture of **1d** (90 mg, 0.42 mmol), methyl 4,6-dichloropyridazine-3-carboxylate (88 mg, 0.42 mmol) and DIPEA (273 mg, 2.12 mmol) in DMF (1 mL) was stirred at 80 °C for 10 h. The reaction was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to give compound **1e** (80 mg, 55% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.45$ min, m/z (M+H)⁺ = 347.1.

Step 5. Methyl 6-(cyclopropanecarboxamido)-4-((4-methoxy-1-methyl-1*H*-indol-3-yl)amino)pyridazine-3-carboxylate (1f)

[00224] A mixture of **1e** (98 mg, 0.28 mmol), cyclopropanecarboxamide (48 mg, 0.57 mmol), Cs₂CO₃ (276 mg, 0.85 mmol), BrettPhos (26 mg, 0.028 mmol) and BrettPhos Pd G3 (15 mg, 28 mmol) in anhydrous 1,4-dioxane (1 mL) was stirred at 80 °C for 6 h. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to give compound **1f** (65 mg, 58% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 0.49$ min, m/z (M+H)⁺ = 396.2.

Step 6. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-1-methyl-1*H*-indol-3-yl)amino)-*N*-methylpyridazine-3-carboxamide (1)

[00225] A mixture of **1f** (50 mg, 0.13 mmol) in methylamine (1.5 mL, 30% alcohol solution) was stirred at 80 °C for 48 h. The mixture was concentrated. The residue was purified by *prep*-HPLC (Method C) to give compound **1** (4 mg, 8% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (s, 1H), 11.02 (s, 1H), 9.02-8.99 (m, 1H), 7.98 (s, 1H), 7.23 (s, 1H), 7.12 (t, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.53 (d, $J = 7.6$ Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.86 (d, $J = 4.8$ Hz, 3H), 2.10-2.06 (m, 1H), 0.83-0.81 (m, 4H). LC-MS (ESI, Method 2) $t_R = 2.43$ min, m/z (M+H)⁺ = 395.2.

Example 2**Step 1. 5-Bromo-4-methoxy-1-methyl-1H-indole-3-carbaldehyde (2b)**

[00226] A mixture of **2a** (1.5 g, 6.3 mmol) and *t*BuOK (1.7 g, 15.6 mmol) in DMF (15 mL) was stirred for 10 min at 0 °C. Then iodomethane (3.5 g, 24.9 mmol) was added to the reaction mixture. After stirring at r.t. for 18 h, the mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic phase was washed with brine (40 mL), concentrated and the residue was purified by flash chromatography on silica gel (PE/DCM = 1/1) to afford **2b** (1.6 g, 96% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.12 (s, 1H), 8.25 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H).

Step 2. 5-Bromo-4-methoxy-1-methyl-1H-indole-3-carboxylic acid (2c)

[00227] A mixture of **2b** (1.2 g, 4.5 mmol) and KMnO₄ (1.4 g, 8.9 mmol) in acetone/H₂O (80 mL, v/v = 1/1) was stirred at r.t. for 10 h. The mixture was filtered and the organic solvent was removed under reduced pressure. The aqueous layer was basified with 1 M NaOH to pH >10 and washed with EtOAc (20 mL). The separated aqueous layer was acidified with 2 M HCl to pH = 5 and extracted with DCM/MeOH (40 mL*3, v/v = 10/1). The combined organic phase was washed with brine (40 mL), concentrated to afford the crude **2c** (0.60 g, 50% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.11 min, *m/z* (⁷⁹Br, M+H)⁺ = 284.0.

Step 3. *Tert*-butyl (5-bromo-4-methoxy-1-methyl-1H-indol-3-yl) carbamate (2d)

[00228] A mixture of **2c** (417 mg, 1.5 mmol), DPPA (444 mg, 1.6 mmol), Et₃N (444 mg, 4.40 mmol) in toluene (4 mL) was stirred at 110 °C for 1 h. Then *t*BuOH (217 mg, 2.9 mmol) was added into the mixture. After stirring at 110 °C for 12 h, the reaction mixture was cooled,

concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 20/1) to afford **2d** (60 mg, 12% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.47 min, m/z (^{79}Br , $\text{M}+\text{H}$) $^+$ = 355.2.

Step 4. 4-((5-Bromo-4-methoxy-1-methyl-1*H*-indol-3-yl) amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃) nicotinamide hydrochloride (2e)

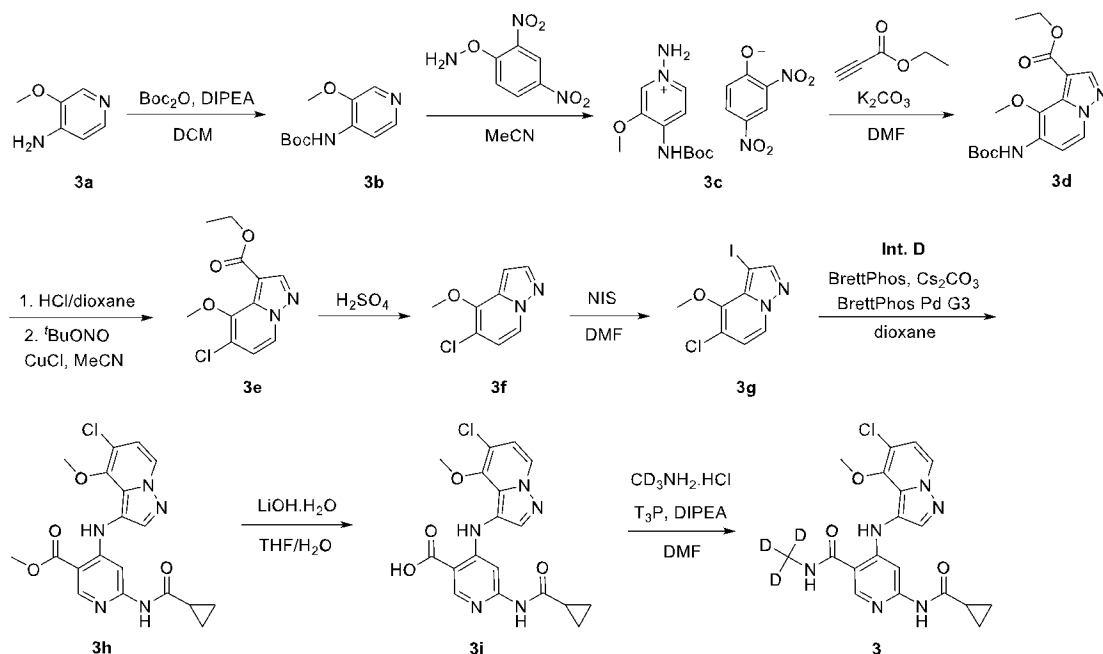
[00229] A mixture of **2d** (55 mg, 0.15 mmol), **Int. A** (40 mg, 0.14 mmol), cat. *conc.* HCl in EtOH (1 mL) was stirred at 90 °C for 18 h. The reaction mixture was cooled, concentrated and purified by *prep*-TLC (DCM/MeOH = 30/1) to afford **2e** (46 mg, 60% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.30 min, m/z (^{79}Br , $\text{M}+\text{H}$) $^+$ = 475.3.

Step 5. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-1-methyl-5-vinyl-1*H*-indol-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (2f)

[00230] A mixture of **2e** (56 mg, 0.11 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (19 mg, 0.13 mmol), CsF (48 mg, 0.315 mmol) and Pd(dppf)Cl₂ (8 mg, 0.01 mmol) in dioxane/H₂O (1.2 mL, v/v=3/1) was stirred at 150 °C for 5 h under microwave under N₂. After cooling to r.t., the mixture was filtered and the residue was concentrated to afford the crude **2f** (40 mg, 90% yield) as a black solid. LC-MS (ESI, Method 3) t_R = 1.26 min, m/z ($\text{M}+\text{H}$) $^+$ = 423.4.

Step 6. 6-(Cyclopropanecarboxamido)-4-((5-ethyl-4-methoxy-1-methyl-1*H*-indol-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (2)

[00231] A mixture of **2f** (40 mg, 0.095 mmol) and Pd/C (4 mg, 0.036 mmol, wetted with ca. 50% water) in MeOH was stirred at r.t under H₂ (0.1 MPa) for 5 h. The mixture was filtered and purified by *prep*-HPLC (Method A) to afford **2** (11.4 mg, 28% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 10.33 (s, 1H), 8.44-8.46 (m, 2H), 7.74 (s, 1H), 7.27 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 2.63 (q, J = 7.6 Hz, 2H), 1.97-1.91 (m, 1H), 1.16 (t, J = 7.6 Hz, 3H), 0.73-0.69 (m, 4H). LC-MS (ESI, Method 2) t_R = 2.58 min, m/z ($\text{M}+\text{H}$) $^+$ = 425.2.

Example 3**Step 1. *Tert*-butyl (3-methoxypyridin-4-yl)carbamate (3b)**

[00232] A solution of **3a** (800 mg, 6.44 mmol), Boc_2O (1.83 g, 8.38 mmol, 1.9 mL) and DIPEA (1.67 g, 12.89 mmol, 2.24 mL) in DCM (15 mL) was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was concentrated and purified by flash chromatography (EA in PE is 10-50%) to give compound **3b** (1.45 g, yield given) as a white solid. LC-MS (ESI, Method 4) t_R = 1.92 min, m/z ($\text{M}+\text{H}$) $^+$ = 225.1.

Step 2. 1-Amino-4-(((*tert*-butoxycarbonyl)amino)-3-methoxypyridin-1-ium 2,4-dinitrophenolate (3c)

[00233] A mixture of **3b** (1.45 g, 6.47 mmol) and *O*-(2,4-dinitrophenyl) hydroxylamine (1.42 g, 7.11 mmol) in MeCN (50 mL) was stirred at 50 °C for 16 h. A yellow solution was formed. The reaction was concentrated to give **3c** (2.73 g, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) t_R = 1.66 min, m/z M^+ = 240.1.

Step 3. Ethyl 5-(((*tert*-butoxycarbonyl)amino)-4-methoxypyrazolo[1,5-*a*]pyridine-3-carboxylate (3d)

[00234] A mixture of ethyl propiolate (685 mg, 6.98 mmol, 0.71 mL), **3c** (1.29 g, 5.37 mmol)

and K_2CO_3 (1.48 g, 10.74 mmol) in DMF (15 mL) was stirred at 20 °C for 2 h. A black suspension was formed. The reaction mixture was concentrated in vacuo and diluted with water (50 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2), brine (50 mL*2), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **3d** (428 mg, 22% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 4.16 min, m/z ($\text{M}+\text{H}$)⁺ = 336.1.

Step 4. Ethyl 5-chloro-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (**3e**)

[00235] To a mixture of **3d** (330 mg, 0.98 mmol) in DCM (2 mL) was added HCl/dioxane (4 M, 2 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. A yellow solution was formed. The reaction mixture was concentrated to give ethyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (231 mg, HCl salt, crude) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.48 min, m/z ($\text{M}+\text{H}$)⁺ = 236.1.

[00236] To a mixture of ethyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (231 mg, HCl salt, crude) in MeCN (5 mL), was added *tert*-butyl nitrite (152 mg, 1.47 mmol, 0.18 mL) at 0 °C and stirred for 10 min. Then CuCl (145.8 mg, 1.47 mmol) was added into the above mixture. The resulting mixture was stirred at 80 °C for 12 h. A yellow solution was formed. The reaction mixture was concentrated and purified by flash chromatograph (EA in PE is 10-30%) to give **3e** (100 mg, 40% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.44 min, m/z ($\text{M}+\text{H}$)⁺ = 255.2.

Step 5. 5-Chloro-4-methoxy-pyrazolo[1,5-*a*]pyridine (**3f**)

[00237] Heat a well-stirred solution of **3e** (100 mg, 0.39 mmol) in 2 mL of 50% H_2SO_4 at 110 °C for 3 h. A yellow solution was formed. Cool down the solution to room temperature. Neutralize the solution with aq. NaOH (1.0 M). Add 40 mL of water to the above solution. Extract the solution by EtOAc (30 mL*3). Combine the organic layer. Dry the organic layer over anhydrous Na_2SO_4 . Filter the organic layer through a pad of Celite. Evaporate the organic layer in vacuum to give **3f** (33 mg, 46% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.20 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.63 (dd, J = 2.4 Hz, 1.2 Hz, 1H), 4.06 (s, 3H). LC-MS (ESI, Method 4) t_R = 2.46 min, m/z ($\text{M}+\text{H}$)⁺ = 183.1.

Step 6. 5-Chloro-3-iodo-4-methoxy-pyrazolo[1,5-*a*]pyridine (3g)

[00238] A mixture of **3f** (31 mg, 0.17 mmol) and NIS (38.2 mg, 0.17 mmol) in DMF (2 mL) was stirred at 20 °C for 12 h. A yellow suspension was formed. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with brine (40 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatograph (EA in PE is 10-30%) to give **3g** (50 mg, 95% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 3.12 min, *m/z* (M+H)⁺ = 308.9.

Step 7. Methyl 4-((5-chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)nicotinate (3h)

[00239] A mixture of **3g** (50 mg, 0.16 mmol), **Int. D** (68 mg, 0.19 mmol, TFA salt), BrettPhos (17.4 mg, 0.032 mmol), Cs₂CO₃ (132 mg, 0.41 mmol) and BrettPhos Pd G3 (14.7 mg, 0.016 mmol) in dioxane (1 mL) was degassed and purged with nitrogen for 3 times. The resulting mixture was stirred at 100 °C under N₂ atmosphere for 24 h. A yellow suspension was formed. The reaction mixture was concentrated and purified by *prep*-TLC (PE/EA = 1/2) to give **3h** (60 mg, 89% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.85 (s, 1H), 9.58 (s, 1H), 8.67 (s, 1H), 8.54 (d, *J* = 7.2 Hz, 1H), 8.15 (s, 1H), 7.64 (s, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 1.98-1.90 (m, 1H), 0.78-0.70 (m, 4H). LC-MS (ESI, Method 4) *t_R* = 2.42 min, *m/z* (M+H)⁺ = 416.2.

Step 8. 4-((5-Chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)nicotinic acid (3i)

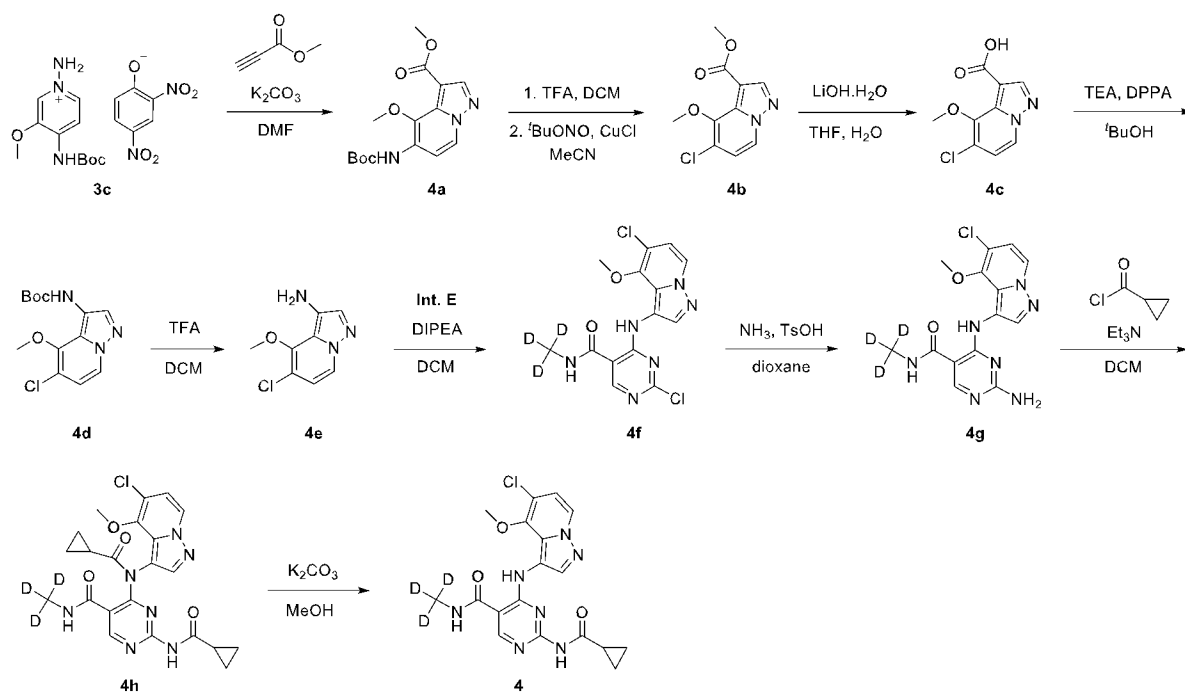
[00240] A mixture of **3h** (60 mg, 0.144 mmol) and LiOH.H₂O (18 mg, 0.433 mmol) in co-solvent of THF (3 mL) and water (1 mL) was stirred at 40 °C for 12 h. A yellow solution was formed. The reaction mixture was concentrated and dried in vacuo to give **3i** (58 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) *t_R* = 1.01 min, *m/z* (M+H)⁺ = 402.2.

Step 9 4-((5-Chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)nicotinamide (3)

[00241] A mixture of CD₃NH₂.HCl (30.5 mg, 0.433 mmol), **3i** (58 mg, crude), DIPEA (93.3 mg, 0.721 mmol, 0.13 mL) and T₃P (275.6 mg, 0.433 mmol, 50% purity in EtOAc) in DMF (2

mL) was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was filtered and purified by *Prep*-HPLC (Method E) to give **3** (3.6 mg, 6% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 10.35 (s, 1H), 8.55 (s, 1H), 8.51-8.43 (m, 2H), 8.11 (s, 1H), 7.65 (s, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 1.98-1.90 (m, 1H), 0.76-0.71 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 1.97 min, *m/z* (M+H)⁺ = 418.2.

Example 4



Step 1. Methyl 5-((*tert*-butoxycarbonyl)amino)-4-methoxypyrazolo[1,5-*a*] pyridine-3-carboxylate (**4a**)

[00242] A mixture of methyl propiolate (749 mg, 8.91 mmol, 7.93 mL), **3c** (1.89 g, 4.45 mmol) and K₂CO₃ (1.23 g, 8.91 mmol) in DMF (5 mL) was stirred at 20 °C for 2 h. A black suspension was formed. The reaction mixture was concentrated and diluted with water (50 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **4a** (350 mg, 24% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.32 (brs, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 1.55 (s, 9H). LC-MS (ESI, Method 4) *t*_R = 4.13 min, *m/z* (M+H)⁺ = 322.1.

Step 2. Methyl 5-chloro-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (4b)

[00243] To a mixture of **4a** (1.25 g, 3.89 mmol) in DCM (5 mL), was added TFA (2 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. A yellow solution was formed. The reaction mixture was concentrated to give methyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (800 mg, TFA salt, crude) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 0.46$ min, m/z (M+H)⁺ = 222.1.

[00244] To a mixture of methyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (800 mg, TFA salt, crude) in MeCN (10 mL), was added *tert*-butyl nitrite (559 mg, 5.42 mmol, 0.65 mL) at 0 °C, and stirred for 10 min. Then CuCl (716 mg, 7.23 mmol) was added into the above mixture, the resulting mixture was stirred at 80 °C for 2 h. A yellow solution was formed. The reaction mixture was concentrated and purified by flash chromatography (EA in PE is 10-30%) to give **4b** (600 mg, 69% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 2.31$ min, m/z (M+H)⁺ = 241.2.

Step 3. 5-Chloro-4-methoxypyrazolo[1,5-*a*]pyridine-3-carboxylic acid (4c)

[00245] A mixture of **4b** (300 mg, 1.25 mmol) and LiOH.H₂O (157 mg, 3.74 mmol) in co-solvent of THF (6 mL) and water (2 mL) was stirred at 70 °C for 12 h. A yellow solution was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL). The aqueous layer was adjusted to pH = 3 with aq. HCl (2 M) and extracted with EtOAc (20 mL*3). The organic layer was concentrated and dried in vacuo to give **4c** (180 mg, 64% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 1.79$ min, m/z (M+H)⁺ = 227.0.

Step 4. *Tert*-butyl (5-chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)carbamate (4d)

[00246] A mixture of **4c** (180 mg, 0.79 mmol), *N,N*-diethylethanamine (161 mg, 1.59 mmol, 0.22 mL) and DPPA (284 mg, 1.03 mmol, 0.22 mL) in *t*BuOH (3 mL) was stirred at 110 °C for 6 h. A yellow suspension was formed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL*3). The combined organic layer was washed with water (100 mL*3), brine (100 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 5-30%) to give **4d** (100 mg, 42% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 2.31$ min, m/z (M+H)⁺ = 298.1.

Step 5. 5-Chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-amine (4e)

[00247] To a mixture of **4d** (100 mg, 0.34 mmol) in DCM (3 mL) was added TFA (1 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. A yellow solution was formed. The reaction mixture was quenched with *sat. aq.* NaHCO₃ (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*3), brine (60 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-60%) to give **4e** (40 mg, 60% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 0.65 min, *m/z* (M+H)⁺ = 198.1.

Step 6. 2-Chloro-4-((5-chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)pyrimidine-5-carboxamide (4f)

[00248] To a mixture of **4e** (40 mg, 0.20 mmol) and **Int. E** (42 mg, 0.20 mmol) in DCM (5 mL), was added DIPEA (52 mg, 0.40 mmol, 0.07 mL) at 0 °C. The resulting mixture was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*3), brine (60 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated to give **4f** (74 mg, 98% yield) as a white solid. LC-MS (ESI, Method 4) *t_R* = 2.88 min, *m/z* (M+H)⁺ = 370.1.

Step 7. 2-Amino-4-((5-chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)pyrimidine-5-carboxamide (4g)

[00249] A mixture of **4f** (20 mg, 0.054 mmol) and TsOH (19 mg, 0.11 mmol) in NH₃/dioxane solution (3 mL, 0.4 M) was stirred at 80 °C for 72 h. A white suspension was formed. The reaction mixture was diluted with water (40 mL) and extracted with DCM (40 mL*3). The combined organic layer was washed with water (40 mL*3), brine (40 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **4g** (12 mg, 63% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 1.87 min, *m/z* (M+H)⁺ = 351.2.

Step 8. 4-(*N*-(5-chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)cyclopropane carboxamido)-2-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)pyrimidine-5-carboxamide (4h)

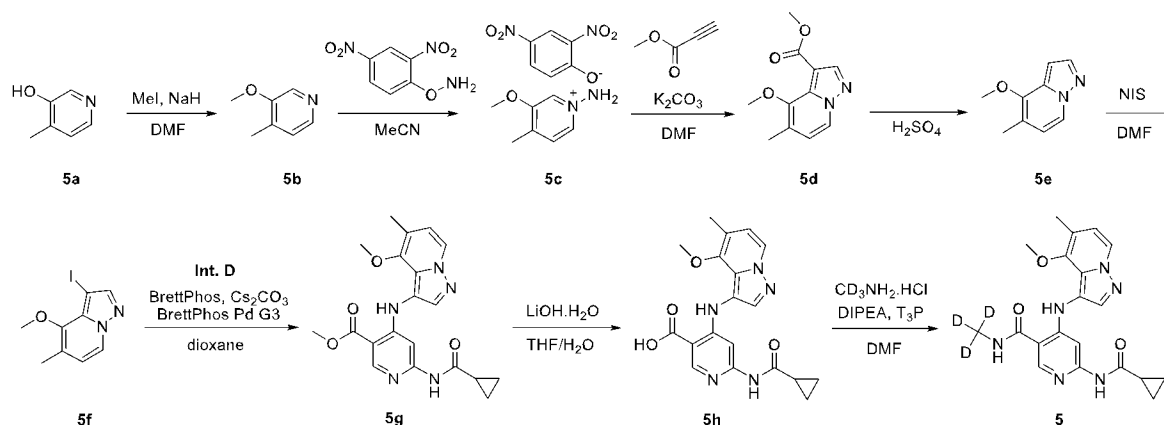
[00250] A mixture of **4g** (12 mg, 0.034 mmol), cyclopropane carbonyl chloride (11 mg, 0.103

mmol) and DIPEA (17 mg, 0.171 mmol, 0.024 mL) in DCM (2 mL) was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was concentrated and dried in vacuo to give **4h** (16 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) $t_R = 2.94$ min, m/z (M+H)⁺ = 487.3.

Step 9. 4-((5-Chloro-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-2-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)pyrimidine-5-carboxamide (4**)**

[00251] A mixture of **4h** (16 mg, crude) and K₂CO₃ (9 mg, 0.066 mmol) in MeOH (3 mL) was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was filtered and purified by *prep*-HPLC (Method D) further lyophilized to give **4** (2.3 mg, 16.7% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.82 (s, 1H), 10.98 (s, 1H), 9.62 (s, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 8.39 (d, $J = 7.2$ Hz, 1H), 6.83 (d, $J = 7.2$ Hz, 1H), 4.09 (s, 3H), 2.15-2.06 (m, 1H), 0.93-0.80 (m, 4H). LC-MS (ESI, Method 4) $t_R = 2.17$ min, m/z (M+H)⁺ = 419.2.

Example 5



Step 1. 3-Methoxy-4-methylpyridine (5b**)**

[00252] To a mixture of **5a** (2.50 g, 22.91 mmol) in DMF (20 mL), was added NaH (1.37 g, 34.36 mmol, 60% in mineral oil) and CH₃I (3.58 g, 25.20 mmol, 1.57 mL) at 0 °C. The resulting mixture was stirred at 20 °C for 2 h. A black suspension was formed. The reaction mixture was diluted with water (100 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **5b** (230 mg, 8% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 8.10 (d, $J =$

4.8 Hz, 1H), 6.72 (m, 1H), 3.90 (s, 3H), 2.21 (s, 3H). LC-MS (ESI, Method 4) t_R = 0.56 min, m/z (M+H)⁺ = 124.0.

Step 2. 1-Amino-3-methoxy-4-methylpyridin-1-ium 2,4-dinitrophenolate (5c)

[00253] A mixture of **5b** (230 mg, 1.87 mmol) and *O*-(2,4-dinitrophenyl) hydroxylamine (409 mg, 2.05 mmol) in MeCN (3 mL) was stirred at 50 °C for 16 h. A yellow solution was formed. The reaction was concentrated to give **5c** (260 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) t_R = 1.16 min, m/z M⁺ = 140.1.

Step 3. Methyl 4-methoxy-5-methylpyrazolo[1,5-*a*]pyridine-3-carboxylate (5d)

[00254] A mixture of methyl propiolate (236 mg, 2.80 mmol, 0.25 mL), **5c** (260 mg, 1.87 mmol) and K₂CO₃ (516 mg, 3.74 mmol) in DMF (3 mL) was stirred at 20 °C for 2 h. A black suspension was formed. The reaction mixture was concentrated in vacuo and diluted with water (50 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **5d** (140 mg, 34% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.60 min, m/z (M+H)⁺ = 221.0.

Step 4. 4-Methoxy-5-methylpyrazolo[1,5-*a*]pyridine (5e)

[00255] A well-stirred solution of **5d** (140 mg, 0.636 mmol) in 2 mL of 50% H₂SO₄ was heated at 110°C for 3 h. A yellow solution was formed. Cool down the solution to room temperature. Neutralize the solution with *aq.* NaOH (1.0 M) using litmus paper as the indicator. Add 40 mL of water to the above solution. Extract the solution by EtOAc (30 mL*3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered through a pad of celite and evaporated to give **5e** (50 mg, 48% yield) as a light-yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, J = 7.2 Hz, 1H), 7.87 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 7.2 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 2.28 (s, 3H). LC-MS (ESI, Method 4) t_R = 2.29 min, m/z (M+H)⁺ = 163.1.

Step 5. 3-Iodo-4-methoxy-5-methylpyrazolo[1,5-*a*]pyridine (5f)

[00256] A mixture of **5e** (50 mg, 0.308 mmol) and NIS (73 mg, 0.324 mmol) in DMF (1 mL) was stirred at 20 °C for 24 h. A yellow suspension was formed. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer

was washed with brine (40 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **5f** (70 mg, 79% yield) as a yellow solid. LCMS (ESI, Method 4) *t_R* = 2.93 min, *m/z* (M+H)⁺ = 289.0. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 6.8 Hz, 1H), 7.85 (s, 1H), 6.59 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 2.32 (s, 3H).

Step 6. Methyl 6-(cyclopropanecarboxamido)-4-((4-methoxy-5-methylpyrazolo [1,5-*a*]pyridin-3-yl)amino)nicotinate (5g)

[00257] A mixture of **5f** (70 mg, 0.243 mmol), **Int. D** (102 mg, 0.29 mmol, TFA salt), BrettPhos (26 mg, 0.049 mmol), Cs₂CO₃ (198 mg, 0.607 mmol) and BrettPhos Pd G3 (22 mg, 0.024 mmol) in dioxane (3 mL) was degassed and purged with nitrogen for 3 times. The resulting mixture was stirred at 100 °C under N₂ atmosphere for 72 h. A yellow suspension was formed. The reaction mixture was concentrated and purified by *prep*-TLC (DCM/MeOH = 10/1) to give **5g** (60 mg, 62% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 2.18 min, *m/z* (M+H)⁺ = 396.3.

Step 7. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-methylpyrazolo[1,5-*a*]pyridin-3-yl)amino)nicotinic acid (5h)

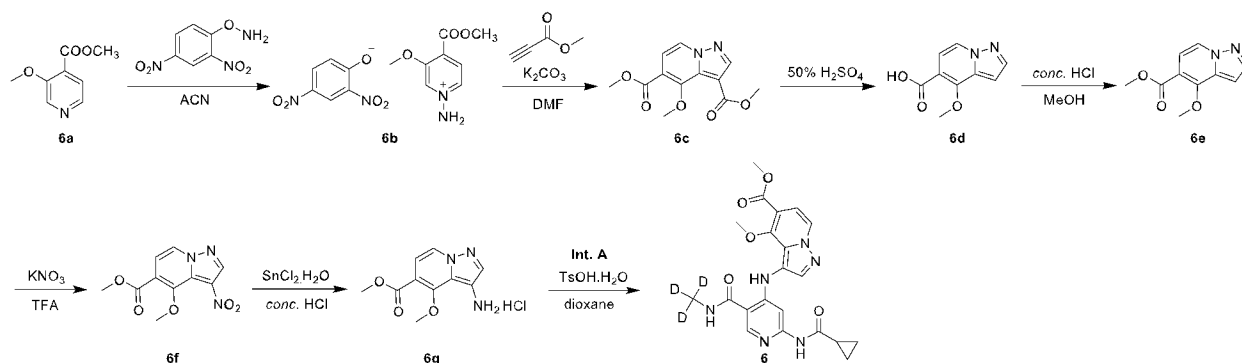
[00258] A mixture of **5g** (60 mg, 0.152 mmol) and LiOH.H₂O (19 mg, 0.455 mmol) in THF (3 mL) and water (1 mL) was stirred at 40 °C for 12 h. A yellow solution was formed. The reaction mixture was concentrated and dried in vacuo to give **5h** (58 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) *t_R* = 1.78 min, *m/z* (M+H)⁺ = 382.2.

Step 8. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-methylpyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (5)

[00259] A mixture of CD₃NH₂.HCl (32 mg, 0.456 mmol), **5h** (58 mg, crude), DIPEA (118 mg, 0.912 mmol, 0.158 mL) and T₃P (290 mg, 0.456 mmol, 50% purity in EtOAc) in DMF (2 mL) was stirred at 20 °C for 12 h. A yellow solution was formed. The reaction mixture was filtered and purified by *prep*-HPLC (Method D) to give **5** (5.2 mg, 9% yield) as a light-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.65 (s, 1H), 10.28 (s, 1H), 8.51 (s, 1H), 8.48 (s, 1H), 8.35 (d, *J* = 6.8 Hz, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 6.73 (d, *J* = 6.8 Hz, 1H), 3.66 (s, 3H), 2.22 (s, 3H),

1.98-1.90 (m, 1H), 0.74-0.70 (m, 4H). LC-MS (ESI, Method 4) $t_R = 1.82$ min, m/z (M+H)⁺ = 398.3.

Example 6



Step 1. 1-Amino-3-methoxy-4-(methoxycarbonyl)pyridin-1-ium 2,4-dinitrophenolate (6b)

[00260] A mixture of **6a** (6.8 g, 40.68 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (9.72 g, 48.82 mmol) in ACN (60 mL) was stirred at 50 °C overnight. The mixture was concentrated to afford **6b** (14.9 g, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) $t_R = 0.46$ min, m/z M⁺ = 183.0.

Step 2. Dimethyl 4-methoxypyrazolo[1,5-a]pyridine-3,5-dicarboxylate (6c)

[00261] A mixture of **6b** (14.9 g, 40.68 mmol), methyl prop-2-ynoate (3.53 g, 42.03 mmol) and K₂CO₃ (10.56 g, 76.43 mmol) in DMF (60 mL) was stirred at 30 °C for 2 h. The reaction mixture was poured into ice-water (200 mL) and extracted with EtOAc (200 mL*2). The combined organic phase was washed with brine (100 mL*2) and concentrated. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 5/1) to afford **6c** (6.62 g, 62% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.10$ min, m/z (M+H)⁺ = 265.2.

Step 3. 4-Methoxypyrazolo[1,5-a]pyridine-5-carboxylic acid (6d)

[00262] A mixture of **6c** (7 g, 26.49 mmol) in *aq.* H₂SO₄ (130 mL, 50% wt in water) was stirred at 85 °C for 4 h. After cooling to r.t., the mixture was diluted with water (200 mL), neutralized with *aq.* NaOH (1 N) to pH = 3. The mixture was extracted with EtOAc (200 mL*3). The compound organic layer was washed with brine (100 mL) and concentrated to afford **6d** (4.4 g, 86% yield) as a brown solid. LC-MS (ESI, Method 3) $t_R = 0.94$ min, m/z (M+H)⁺ = 193.1.

Step 4. Methyl 4-methoxypyrazolo[1,5-*a*]pyridine-5-carboxylate (6e)

[00263] To a solution of **6d** (4.4 g, 22.90 mmol) in MeOH (250 mL) was added *conc.* HCl (3.75 mL, 46 mmol). After stirring for 18 h at 80 °C, the mixture was concentrated and the residue was diluted with DCM (20 mL). The solution was washed with *sat.* NaHCO₃ (20 mL) and the aqueous layer was extracted with DCM (20 mL*2). The combined organic layer was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to afford **6e** (2.76 g, 58% yield) as a yellow solid. LC-MS (ESI, Method 3) *t_R* = 1.14 min, *m/z* (M+H)⁺ = 207.1.

Step 5. Methyl 4-methoxy-3-nitropyrzolo[1,5-*a*]pyridine-5-carboxylate (6f)

[00264] To a solution of **6e** (500 mg, 2.42 mmol) in TFA (5 mL) was added KNO₃ (245 mg, 2.42 mmol) at r.t. and the mixture was stirred at 35 °C for 3 h. The solvent was removed by pumping through N₂. The mixture was basified with *sat.* Na₂CO₃ to pH > 8 and extracted with EtOAc (5 mL*3). The organic layer was concentrated and purified by flash chromatography (PE/EA = 3/1) to afford the crude product. The crude product was triturated with EtOAc (3 mL). The formed solid was filtered and dried to afford **6f** (300 mg, 49% yield) as a yellow solid. LC-MS (ESI, Method 3) *t_R* = 1.06 min, *m/z* (M+H)⁺ = 252.2.

Step 6. Methyl 3-amino-4-methoxypyrazolo[1,5-*a*]pyridine-5-carboxylate hydrochloride (6g)

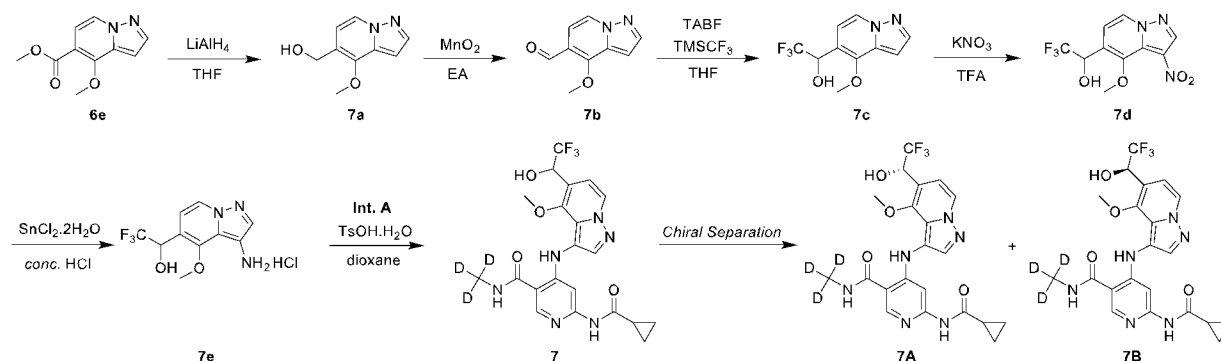
[00265] To a solution of **6f** (200 mg, 0.79 mmol) in *conc.* HCl (4 mL) was added SnCl₂·2H₂O (359 mg, 1.59 mmol) at 0 °C and the mixture was stirred at 0 °C for 2 h. The formed solid was filtered and dried to afford **6g** (150 mg, 73% yield) as a yellow solid. LC-MS (ESI, Method 3) *t_R* = 0.53 min, *m/z* (M+H)⁺ = 222.0.

Step 7. Methyl 3-((2-(cyclopropanecarboxamido)-5-((methyl-*d*₃)carbamoyl)pyridin-4-yl)amino)-4-methoxypyrazolo[1,5-*a*]pyridine-5-carboxylate (6)

[00266] To a solution of **6g** (150 mg, 0.58 mmol) and **Int. A** (149 mg, 0.58 mmol) in dioxane (2 mL) was added TsOH·H₂O (22 mg, 0.12 mmol) and stirred at 100 °C for 12 h. The reaction mixture was concentrated and purified by flash chromatography on silical gel (DCM/MeOH = 10/1) to afford **6** (110 mg, 43% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.76 (s, 1H), 10.68 (s, 1H), 8.56 (s, 1H), 8.51 (s, 1H), 8.44 (d, *J* = 7.2 Hz, 1H), 8.18 (s, 1H), 7.87 (s,

1H), 7.07 (d, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 2.03-1.92 (m, 1H), 0.80-0.70 (m, 4H).
LC-MS (ESI, Method 3) $t_R = 1.05$ min, m/z ($M+H$)⁺ = 442.1.

Example 7



Step 1. (4-Methoxypyrazolo[1,5-a]pyridin-5-yl)methanol (7a)

[00267] To a solution of **6e** (1.3 g, 6.30 mmol) in THF (15 mL) was added LiAlH₄ (455 mg, 11.98 mmol) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched with aqueous solution of seignette salt (10 mL) and extracted with EtOAc (15 mL*2). The combined organic layer was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 2/1) to afford **7a** (1.07 g, 95% yield) as a white solid. LC-MS (ESI, Method 3) $t_R = 0.94$ min, m/z ($M+H$)⁺ = 179.0.

Step 2. 4-Methoxypyrazolo[1,5-a]pyridine-5-carbaldehyde (7b)

[00268] To a solution of **7a** (1.0 g, 5.62 mmol) in EtOAc (10 mL) was added MnO₂ (2.92 g, 33.68 mmol) at r.t. After stirring for 4 h at 80 °C, the mixture was filtered and the filtrate was concentrated to afford **7b** (800 mg, 81% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.02$ min, m/z ($M+H$)⁺ = 177.3.

Step 3. 2,2,2-Trifluoro-1-(4-methoxypyrazolo[1,5-a]pyridin-5-yl)ethan-1-ol (7c)

[00269] To a solution of **7b** (620 mg, 3.52 mmol) and trimethyl(trifluoromethyl)silane (1.10 g, 7.74 mmol) in THF (10 mL) was added TBAF (0.2 mL, 0.2 mmol, 1.0 M in THF) at 0 °C. The mixture was stirred at 0 °C for 1 h and at 25 °C for 16 h. Then 1 M HCl solution was added and the reaction was stirred at 25 °C for 2 h. The mixture was adjusted to pH = 8 with aq. NaOH (1 M). The mixture was extracted with EtOAc (5 mL*3). The organic layer was concentrated and the residue was purified by flash chromatography (PE/EA = 3/1) to afford **7c** (834 mg, 96%

yield) as a yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.52 (d, $J = 6.8$ Hz, 1H), 8.04 (d, $J = 2.4$ Hz, 1H), 6.97-6.88 (m, 3H), 5.48-5.45 (m, 1H), 4.03 (s, 3H). LC-MS (ESI, Method 3) $t_R = 1.09$ min, m/z ($\text{M}+\text{H}$) $^+ = 247.2$.

Step 4. 2,2,2-Trifluoro-1-(4-methoxy-3-nitropyrrazolo[1,5-*a*]pyridin-5-yl)ethan-1-ol (7d)

[00270] A mixture of **7c** (210 mg, 0.85 mmol) and KNO_3 (95 mg, 0.94 mmol) in TFA (3 mL) was stirred at 30 °C for 2 h. The solvent was removed with pumping through N_2 . The residue was dissolved in EtOAc (5 mL) and basified with *sat.* Na_2CO_3 solution (10 mL) to pH = 9. The mixture was extracted with EtOAc (10 mL*2). The combined organic phase was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 19/1) to afford **7d** (150 mg, 60% yield) as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.96 (s, 1H), 8.86 (d, $J = 6.8$ Hz, 1H), 7.35 (d, $J = 7.2$ Hz, 1H), 7.31 (d, $J = 6.0$ Hz, 1H), 5.62-5.55 (m, 1H), 3.80 (s, 3H). LC-MS (ESI, Method 3) $t_R = 1.12$ min, m/z ($\text{M}+\text{H}$) $^+ = 292.1$.

Step 5. 1-(3-Amino-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethan-1-ol hydrochloride (7e)

[00271] To a mixture of **7d** (200 mg, 0.69 mmol) in *conc.* HCl (4 mL) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (620 mg, 2.75 mmol) at 0 °C. After stirring at 10 °C for 1 h, the reaction mixture was filtered. The filter cake was dried under vacuum to afford **7e** (150 mg, 66% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 0.85$ min, m/z ($\text{M}+\text{H}$) $^+ = 262.0$.

Step 6. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (7)

[00272] A mixture of **7e** (193 mg, 0.59 mmol), **Int. A** (151 mg, 0.59 mmol) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (45 mg, 0.24 mmol) in 1,4-dioxane (3 mL) was stirred at 100 °C for 16 h in a sealed tube. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 9/1) to afford the crude product. The crude product was purified by *prep*-HPLC (Method A) to afford **7** (250 mg, 88% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.68 (s, 1H), 10.36 (s, 1H), 8.55 (s, 1H), 8.51-8.49 (m, 2H), 8.11 (s, 1H), 7.68 (s, 1H), 7.02 (d, $J = 5.6$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 5.43-5.36 (m, 1H), 3.72 (s, 3H), 1.99-1.90 (m, 1H), 0.76-0.67 (m, 4H). LC-MS (ESI, Method 2) $t_R = 3.15$ min, m/z ($\text{M}+\text{H}$) $^+ = 482.0$.

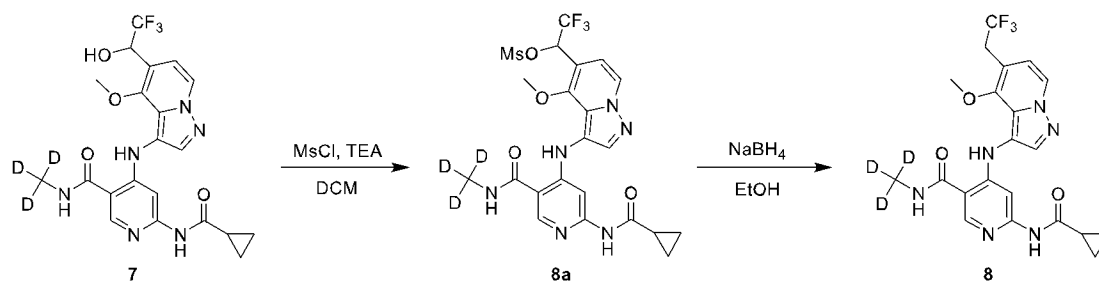
Step 7. (*S*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (7A) and (*R*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (7B)

[00273] Compound **7** (520 mg, 1.08 mmol) was separated by chiral *prep*-HPLC (Method F) to obtain **7A** (204.2 mg, 39% yield) as a white solid and **7B** (206.1 mg, 40% yield) as a white solid.

[00274] **7A**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 10.36 (s, 1H), 8.54 (s, 1H), 8.51-8.49 (m, 2H), 8.11 (s, 1H), 7.68 (s, 1H), 7.01 (d, *J* = 5.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 5.45-5.32 (m, 1H), 3.72 (s, 3H), 1.97-1.90 (m, 1H), 0.74-0.71 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 2.39 min, *m/z* (M+H)⁺ = 482.1. HPLC (Method 5) *t*_R = 10.03 min. The chirality of **7A** was identified by microcrystal electron diffraction method with L-tartaric acid as ligand.

[00275] **7B**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 10.36 (s, 1H), 8.54 (s, 1H), 8.51-8.49 (m, 2H), 8.11 (s, 1H), 7.68 (s, 1H), 7.01 (d, *J* = 6.0 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 5.41-5.30 (m, 1H), 3.72 (s, 3H), 1.97-1.90 (m, 1H), 0.74-0.71 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 2.40 min, *m/z* (M+H)⁺ = 482.1. HPLC (Method 5) *t*_R = 12.27 min.

Example 8



Step 1. 1-(3-((2-(Cyclopropanecarboxamido)-5-((methyl-*d*₃)carbamoyl)pyridin-4-yl)amino)-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethyl methanesulfonate (8a)

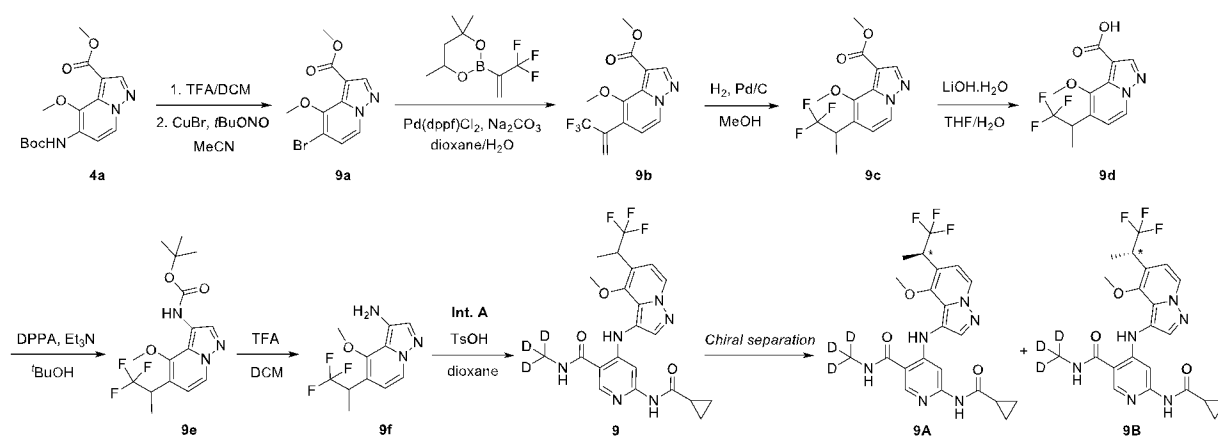
[00276] To a solution of **7** (80 mg, 0.17 mmol) and TEA (100 mg, 1.00 mmol, 0.14 mL) in DCM (1 mL) was added MsCl (29 mg, 0.50 mmol) at 0 °C. Then the mixture was stirred at 14 °C for 30 min. The reaction was quenched with ice-water (3 mL), extracted with DCM (5 mL*3). The combined organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated to afford **8a** (90 mg, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) *t*_R = 1.12 min, *m/z* (M+H)⁺ =

560.2.

Step 2. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoroethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (8)

[00277] To a solution of **8a** (90 mg, 0.16 mmol) in EtOH (1 mL) was added NaBH₄ (9 mg, 0.24 mmol) at 0 °C, then the mixture was stirred at 15 °C for 18 h. The reaction mixture was quenched with ice-water (3 mL) and extracted with EtOAc (5 mL*2). The combined organic layer was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **8** (3.5 mg, 5% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 10.35 (s, 1H), 8.55 (s, 1H), 8.51-8.48 (m, 2H), 8.10 (s, 1H), 7.69 (s, 1H), 6.83 (d, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 3.74-3.65 (m, 2H), 1.96-1.93 (m, 1H), 0.75-0.72 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 2.91 min, *m/z* (M+H)⁺ = 466.1.

Example 9



Step 1. Methyl 5-bromo-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (9a)

[00278] To a mixture of **4a** (2.20 g, 6.85 mmol) in DCM (10 mL), was added TFA (10 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. A yellow solution was formed. The reaction mixture was concentrated to give methyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (1.51 g, TFA salt, crude) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 1.38 min, *m/z* (M+H)⁺ = 222.1.

[00279] To a mixture of methyl 5-amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-3-carboxylate (1.51 mg, TFA salt, crude) in MeCN (10 mL), was added *tert*-butyl nitrite (1.06 g, 10.24 mmol, 1.22 mL) at 0 °C, and stirred for 10 min. Then CuBr (1.96 g, 13.65 mmol) was added into the

above mixture, the resulting mixture was stirred at 80 °C for 2 h. A yellow solution was formed. The reaction mixture was concentrated and purified by flash chromatography (EA in PE is 10-30%) to give **9a** (300 mg, 15% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 2.53$ min, m/z (^{79}Br , $M+H$) $^+ = 285.0$.

Step 2. Methyl 4-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (9b)

[00280] A mixture of **9a** (80 mg, 0.281 mmol), 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (86 mg, 0.365 mmol), Na_2CO_3 (89 mg, 0.842 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (46 mg, 0.056 mmol) in dioxane (2 mL) and water (0.2 mL) was degassed and purged with nitrogen for 3 times. The resulting mixture was stirred at 100 °C under N_2 atmosphere for 1 h. A yellow suspension was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (50 mL*3), brine (50 mL*2), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 0-20%) to give **9b** (84 mg, 99% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 2.91$ min, m/z ($M+H$) $^+ = 301.1$.

Step 3. Methyl 4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (9c)

[00281] To a solution of **9b** (84 mg, 0.28 mmol) in MeOH (5 mL), was added Pd/C (8 mg, 10% wt%, 10% Pd (dry basis), wetted with 55% H_2O). The reaction mixture was degassed and purged with hydrogen for 3 times. The resulting mixture was stirred at 40 °C under H_2 atmosphere for 24 h. A black suspension was formed. The reaction mixture was filtered and concentrated to give **9c** (80 mg, 99% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 2.93$ min, m/z ($M+H$) $^+ = 303.2$.

Step 4. 4-Methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylic acid (9d)

[00282] A mixture of **9c** (80 mg, 0.26 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (89 mg, 2.12 mmol) in co-solvent of THF (3 mL) and water (1 mL) was stirred at 70 °C for 24 h. A yellow solution was formed. The reaction mixture was diluted with water (30 mL), extracted with EtOAc (20 mL) and the organic layer was discarded. The aqueous layer was adjusted to pH = 3 with *aq.* HCl (2

M), then extracted with EtOAc (20 mL*3). The organic layer was concentrated and dried in vacuo to give **9d** (76 mg, 99% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 2.35$ min, m/z (M+H)⁺ = 289.1.

Step 5. *Tert*-butyl (4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl)carbamate (9e)

[00283] A mixture of **9d** (80 mg, 0.28 mmol), *N,N*-diethylethanamine (56 mg, 0.56 mmol, 0.08 mL) and DPPA (99 mg, 0.36 mmol, 0.08 mL) in *t*BuOH (1 mL) was stirred at 110 °C for 6 h. A yellow suspension was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (50 mL*3), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 5-30%) to give **9e** (20 mg, 20% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 3.20$ min, m/z (M+H)⁺ = 360.2.

Step 6. 4-Methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridin-3-amine (9f)

[00284] To a mixture of **9e** (20 mg, 0.056 mmol) in DCM (3 mL), was added TFA (1 mL) at 20 °C. The resulting mixture was stirred at 20 °C for 1 h. A yellow solution was formed. The reaction mixture was quenched with *sat. aq.* NaHCO₃ (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*3), brine (60 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-60%) to give **9f** (12 mg, 83% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 1.87$ min, m/z (M+H)⁺ = 260.2.

Step 7. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (9)

[00285] A mixture of **9f** (10 mg, 0.039 mmol), **Int. A** (10 mg, 0.039 mmol) and TsOH (7 mg, 0.041 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. A yellow solution was formed. The reaction mixture was filtered and purified by *prep*-HPLC (Method E) to give **9** (3.7 mg, 20% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 10.36 (s, 1H), 8.55 (s, 1H), 8.52-8.49 (m, 2H), 8.10 (s, 1H), 7.69 (s, 1H), 6.86 (d, $J = 7.2$ Hz, 1H), 4.16-4.07 (m, 1H), 3.68 (s, 3H), 1.98-1.90 (m, 1H), 1.44 (d, $J = 7.2$ Hz, 3H), 0.74-0.70 (m, 4H). LC-MS (ESI, Method 4) $t_R = 2.27$ min, m/z (M+H)⁺ = 480.3.

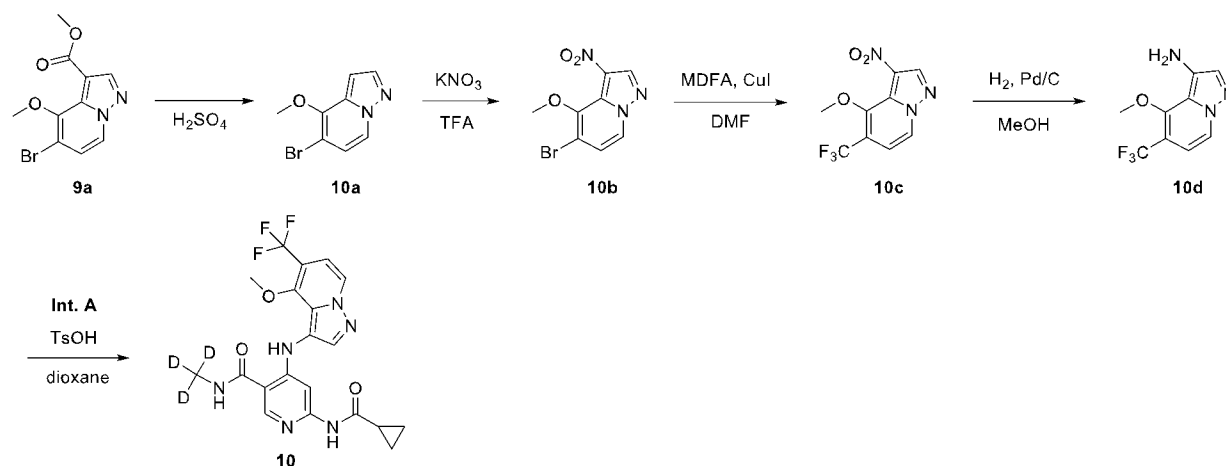
Step 8. (*R) -6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (9A) and (*S**)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (9B)**

[00286] Compound **9** (24 mg, 0.05 mmol) was separated by chiral *prep*-HPLC (Method I) to obtain **9A** (9.5 mg, 40% yield) as a white solid and **9B** (9.1 mg, 38% yield) as a white solid.

[00287] **9A**: LC-MS (ESI, Method 4) $t_R = 2.26$ min, m/z ($M+H$)⁺ = 480.2. HPLC (Method 6) $t_R = 6.42$ min.

[00288] **9B**: LC-MS (ESI, Method 4) $t_R = 2.27$ min, m/z ($M+H$)⁺ = 480.3. HPLC (Method 6) $t_R = 11.56$ min.

Example 10



Step 1. 5-Bromo-4-methoxy-pyrazolo[1,5-*a*]pyridine (10a)

[00289] Heat a well-stirred solution of **9a** (285 mg, 1.00 mmol) in 5 mL of 50% H₂SO₄ at 110°C for 3 h. A yellow solution was formed. Cool down the solution to room temperature. Neutralize the solution with *aq.* NaOH (1.0 M) using litmus paper as the indicator. Add 40 mL of water to the above solution. Extract the solution by EtOAc (30 mL*3). Combine the organic layer. Dry the organic layer over anhydrous Na₂SO₄. Filter the organic layer through a pad of celite. Evaporate the solvent in vacuum to give **10a** (220 mg, 97% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (dd, $J = 7.2$ Hz, 1.2 Hz, 1H), 7.91 (d, $J = 2.4$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 6.63 (dd, $J = 2.4$ Hz, 0.8 Hz, 1H), 4.05 (s, 3H). LC-MS (ESI, Method 4) $t_R = 2.54$ min, m/z (^{79}Br , $M+H$)⁺ = 227.0.

Step 2. 5-Bromo-4-methoxy-3-nitro-pyrazolo[1,5-*a*]pyridine (10b)

[00290] A mixture of **10a** (100 mg, 0.44 mmol) and KNO₃ (40 mg, 0.40 mmol) in TFA (3 mL) was stirred at 30 °C for 2 h. A yellow solution was formed. The reaction mixture was diluted with EtOAc (30 mL), quenched with *aq.* NaHCO₃ (50 mL), separated and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (50 mL*3), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 5-30%) to give **10b** (100 mg, 83% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 2.53 min, *m/z* (⁷⁹Br, M+H)⁺ = 272.0.

Step 3. 4-Methoxy-3-nitro-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyridine (10c)

[00291] A mixture of **10b** (80 mg, 0.29 mmol), CuI (67 mg, 0.35 mmol) and MDFA (85 mg, 0.44 mmol) in DMF (1 mL) was stirred at 100 °C for 12 h. A yellow suspension was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (50 mL*3), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 5-30%) to give **10c** (60 mg, 78% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 8.47 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.2 Hz, 1H), 4.01 (s, 3H). LC-MS (ESI, Method 4) *t_R* = 2.75 min, *m/z* (M+H)⁺ = 262.1.

Step 4. 4-Methoxy-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyridin-3-amine (10d)

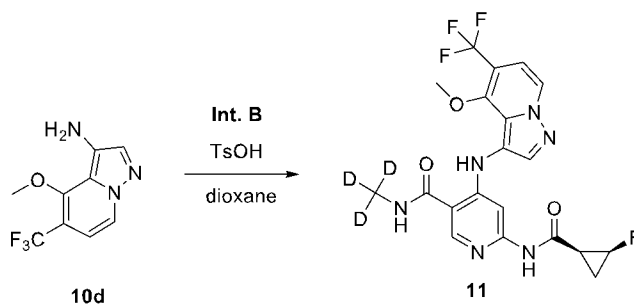
[00292] To a solution of **10c** (60 mg, 0.23 mmol) in MeOH (5 mL), was added Pd/C (6 mg, 10% wt%, 10% Pd (dry basis), wetted with 55% H₂O). The equipment was degassed and purged with hydrogen for 3 times. The resulting mixture was stirred at 40 °C under H₂ atmosphere for 24 h. A black suspension was formed. The reaction mixture was filtered and concentrated to give **10d** (27 mg, 51% yield) as a yellow solid. LC-MS (ESI, Method 4) *t_R* = 1.92 min, *m/z* (M+H)⁺ = 232.1.

Step 5. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (10)

[00293] A mixture of **10d** (27 mg, 0.12 mmol), **Int. A** (29 mg, 0.12 mmol) and TsOH (24 mg, 0.14 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. A yellow solution was formed. The reaction mixture was filtered and purified by flash chromatography (MeOH in DCM is 0-10%)

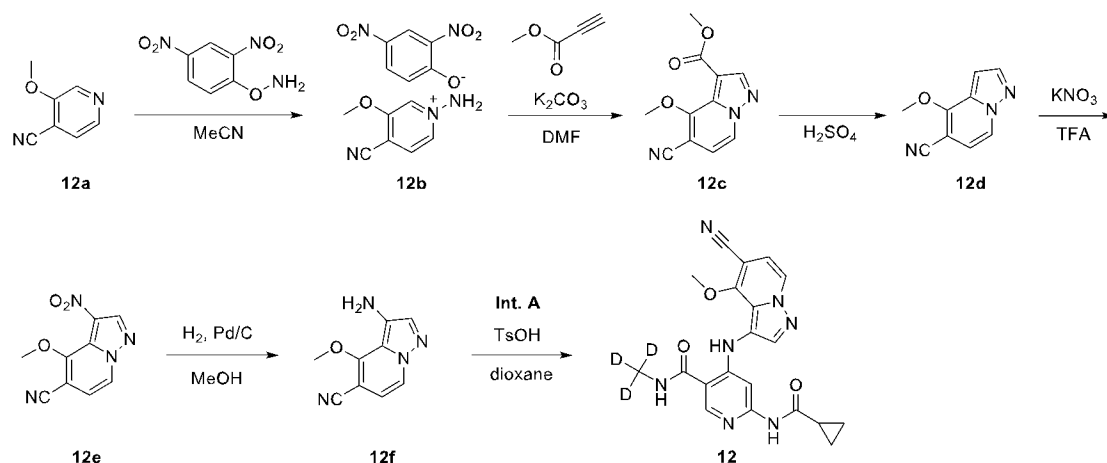
and further triturated with MeCN to give **10** (9.7 mg, 18% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.74 (s, 1H), 10.48 (s, 1H), 8.63-8.59 (m, 2H), 8.52 (s, 1H), 8.25 (s, 1H), 7.73 (s, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 3.81 (s, 3H), 1.98-1.90 (m, 1H), 0.76-0.71 (m, 4H). LC-MS (ESI, Method 4) $t_R = 2.15$ min, m/z ($M+H$) $^+ = 452.3$.

Example 11



Step 1. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl- d_3)nicotinamide (**11**)

[00294] A mixture of **10d** (16 mg, 0.068 mmol), **Int. B** (15 mg, 0.055 mmol) and TsOH (14 mg, 0.082 mmol) in dioxane (1 mL) was stirred at 100 °C for 6 h. A yellow suspension was formed. The reaction mixture was diluted with *aq.* NaHCO₃ (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*2), brine (60 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) and recrystallized in MeCN to give **11** (17.4 mg, 66% yield) as a light-yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.74 (s, 1H), 10.46 (s, 1H), 8.59-8.55 (m, 2H), 8.49 (s, 1H), 8.23 (s, 1H), 7.69 (s, 1H), 6.97 (d, $J = 7.2$ Hz, 1H), 4.93-4.72 (m, 1H), 3.78 (s, 3H), 2.14-2.06 (m, 1H), 1.56-1.43 (m, 1H), 1.11-1.02 (m, 1H). LC-MS (ESI, Method 4) $t_R = 2.22$ min, m/z ($M+H$) $^+ = 470.2$.

Example 12**Step 1. 1-Amino-4-cyano-3-methoxypyridin-1-ium 2,4-dinitrophenolate (12b)**

[00295] A mixture of **12a** (500 mg, 3.73 mmol) and *O*-(2,4-dinitrophenyl) hydroxylamine (816 mg, 4.10 mmol) in MeCN (10 mL) was stirred at 50 °C for 16 h. A yellow solution was formed. The reaction was concentrated to give **12b** (559 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) t_R = 0.64 min, m/z M^+ = 150.1.

Step 2. Methyl 5-cyano-4-methoxypyrazolo[1,5-*a*]pyridine-3-carboxylate (12c)

[00296] A mixture of methyl propiolate (626 mg, 7.45 mmol, 0.66 mL), **12b** (559 mg, 3.72 mmol) and K_2CO_3 (1.03 g, 7.45 mmol) in DMF (10 mL) was stirred at 20 °C for 2 h. A black suspension was formed. The reaction mixture was concentrated in vacuo and diluted with water (50 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2), brine (50 mL*2), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **12c** (400 mg, 46% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.32 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 4.29 (s, 3H), 3.92 (s, 3H). LC-MS (ESI, Method 4) t_R = 2.18 min, m/z $(M+H)^+$ = 232.1.

Step 3. 4-Methoxypyrazolo[1,5-*a*]pyridine-5-carbonitrile (12d)

[00297] Heat a well-stirred solution of **12c** (50 mg, 0.216 mmol) in 1 mL of 50% H_2SO_4 at 100°C for 1 h. A brown solution was formed. Cool down the solution to room temperature.

Neutralize the solution with *aq.* NaOH (1.0 M) using litmus paper as the indicator. Add 40 mL of water to the above solution. Extract the solution by EtOAc (30 mL*3). Combine the organic layer. Dry the organic layer over anhydrous Na₂SO₄. Filter the organic layer through a pad of celite. Evaporate the organic layer in vacuum to give **12d** (20 mg, 53% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 2.4 Hz, 0.8 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 4.40 (s, 3H). LC-MS (ESI, Method 4) *t*_R = 2.07 min, *m/z* (M+H)⁺ = 174.2.

Step 4. 4-Methoxy-3-nitro-pyrazolo[1,5-*a*]pyridine-5-carbonitrile (**12e**)

[00298] A mixture of **12d** (20 mg, 0.115 mmol) in TFA (1 mL) was added KNO₃ (11 mg, 0.11 mmol) at 20 °C. The resulting mixture was stirred at 30 °C for 2 h. A yellow solution was formed. The reaction mixture was quenched with *aq.* NaHCO₃ (50 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with brine (40 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **12e** (20 mg, 79% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 2.19 min, *m/z* (M+H)⁺ = 219.1.

Step 5. 3-Amino-4-methoxy-pyrazolo[1,5-*a*]pyridine-5-carbonitrile (**12f**)

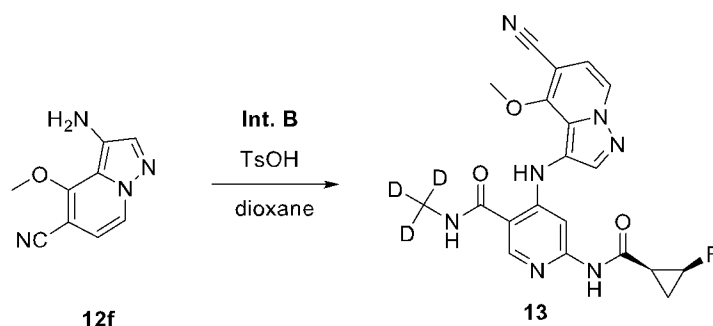
[00299] A mixture of **12e** (20 mg, 0.092 mmol) and Pd/C (5 mg, 10% Pd (dry basis), wetted with 55% H₂O) in MeOH (3 mL) was degassed and purged with hydrogen for 3 times. The resulting mixture was stirred at 40 °C under H₂ atmosphere for 12 h. A black suspension was formed. The reaction mixture was filtered and concentrated to give **12f** (12 mg, 70% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 0.62 min, *m/z* (M+H)⁺ = 189.1. ¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 7.2 Hz, 1H), 7.50 (s, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 4.41 (s, 3H).

Step 6. 4-((5-Cyano-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)nicotinamide (**12**)

[00300] A mixture of **12f** (12 mg, 0.064 mmol), **Int. A** (13 mg, 0.051 mmol) and TsOH (13 mg, 0.076 mmol) in dioxane (2 mL) was stirred at 100 °C for 6 h. A yellow suspension was formed. The reaction mixture was diluted with *aq.* NaHCO₃ (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*2), brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash

chromatography (MeOH in DCM is 0-10%) and recrystallized in MeOH to give **12** (9.0 mg, 34% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.89 (s, 1H), 10.81 (s, 1H), 8.58 (s, 1H), 8.52 (s, 1H), 8.41 (d, $J = 7.2$ Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 6.94 (d, $J = 7.2$ Hz, 1H), 4.25 (s, 3H), 2.01-1.94 (m, 1H), 0.80-0.77 (m, 4H). LC-MS (ESI, Method 4) $t_R = 1.87$ min, m/z (M+H) $^+ = 409.3$.

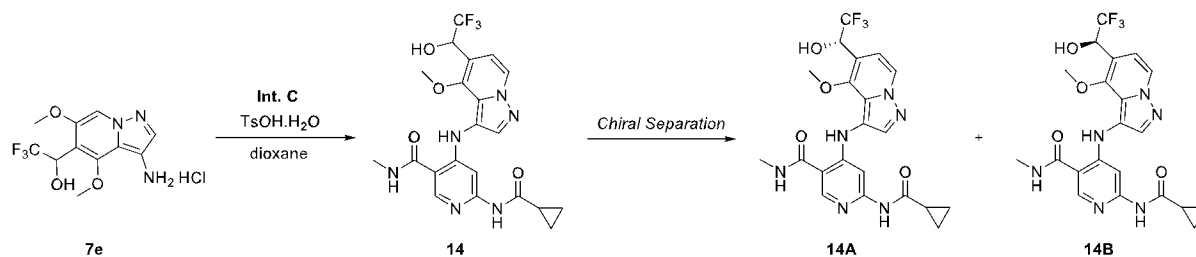
Example 13



Step 1. 4-((5-Cyano-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl- d_3)nicotinamide (**13**)

[00301] A mixture of **12f** (18 mg, 0.096 mmol), **Int. B** (21 mg, 0.076 mmol) and TsOH (20 mg, 0.115 mmol) in dioxane (2 mL) was stirred at 100 °C for 6 h. A yellow suspension was formed. The reaction mixture was diluted with *aq.* NaHCO₃ (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*2), brine (100 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) and recrystallized in MeCN to give **13** (23.4 mg, 72% yield) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (s, 1H), 10.85 (s, 1H), 8.60 (s, 1H), 8.53 (s, 1H), 8.42 (d, $J = 7.2$ Hz, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 6.95 (d, $J = 7.2$ Hz, 1H), 5.00-4.79 (m, 1H), 4.25 (s, 3H), 2.22-2.14 (m, 1H), 1.66-1.55 (m, 1H), 1.18-1.09 (m, 1H). LC-MS (ESI, Method 4) $t_R = 1.85$ min, m/z (M+H) $^+ = 427.2$.

Example 14



Step 1. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-methylnicotinamide (**14**)

[00302] A solution of **7e** (150 mg, 0.46 mmol), **Int. C** (116 mg, 0.46 mmol) and TsOH.H₂O (38 mg, 0.20 mmol) in dioxane (3 mL) was stirred at 100 °C for 16 h. After cooling to r.t., the mixture was concentrated and the residue was purified by chromatography column on silica gel (DCM/MeOH = 20/1) to afford **14** (136 mg, 62% yield) as a white solid. LC-MS (ESI, Method 3) *t_R* = 1.08 min, *m/z* (M+H)⁺ = 479.2.

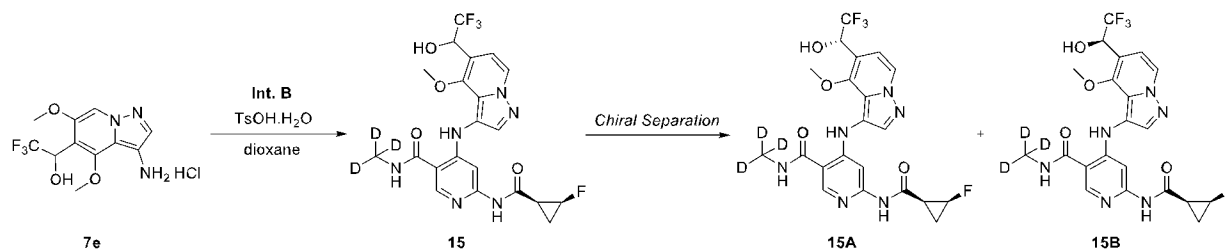
Step 2. (*S*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-methylnicotinamide (**14A**) and (*R*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-methylnicotinamide (**14B**)

[00303] Compound **14** (136 mg, 0.28 mmol) was separated by chiral *prep*-HPLC (Method F) to afford **14A** (43 mg, 32% yield) as a white solid and **14B** (39 mg, 29% yield) as a white solid.

[00304] **14A**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 10.34 (s, 1H), 7.56 (d, *J* = 4.4 Hz, 1H), 8.51-8.49 (m, 2H), 8.11 (s, 1H), 7.68 (s, 1H), 7.02 (d, *J* = 5.6 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 5.41-5.37 (m, 1H), 3.72 (s, 3H), 2.80 (d, *J* = 4.4 Hz, 3H), 1.94-1.92 (m, 1H), 0.73-0.71 (m, 4H). LC-MS (ESI, Method 2) *t_R* = 2.39 min, *m/z* (M+H)⁺ = 479.2. HPLC (Method 5) *t_R* = 8.98 min.

[00305] **14B**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 10.35 (s, 1H), 7.56 (d, *J* = 4.4 Hz, 1H), 8.51-8.49 (m, 2H), 8.11 (s, 1H), 7.68 (s, 1H), 7.03 (d, *J* = 5.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 5.41-5.38 (m, 1H), 3.72 (s, 3H), 2.80 (d, *J* = 4.4 Hz, 3H), 1.95-1.92 (m, 1H), 0.74-0.72 (m, 4H). LC-MS (ESI, Method 2) *t_R* = 2.39 min, *m/z* (M+H)⁺ = 479.2. HPLC (Method 5) *t_R* = 10.89 min.

Example 15



Step 1. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (**15**)

[00306] A mixture of **7e** (252 mg, 0.77 mmol), **Int. B** (210 mg, 0.77 mmol) and TsOH.H₂O (58 mg, 0.31 mmol) in 1,4-dioxane (2 mL) was stirred at 100 °C for 12 h. After cooling to r.t., the mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **15** (170 mg, 45% yield) as a white solid. LC-MS (ESI, Method 3) *t*_R = 1.06 min, *m/z* (M+H)⁺ = 500.2.

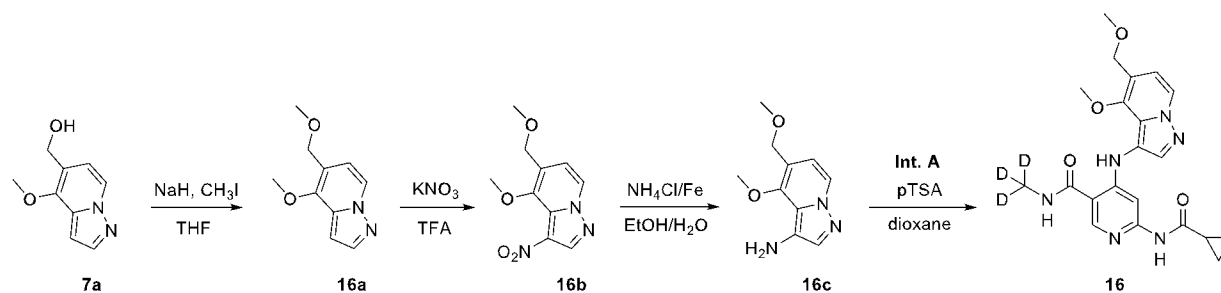
Step 2. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (**15A**) and 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (**15B**)

[00307] Compound **15** (170 mg, 0.34 mmol) was separated by chiral *prep*-HPLC (Method F) to afford **15A** (66 mg, 17% yield) as a white solid and **15B** (73 mg, 19% yield) as a white solid.

[00308] **15A**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 10.37 (s, 1H), 8.55 (s, 1H), 8.52-8.50 (m, 2H), 8.13 (s, 1H), 7.68 (s, 1H), 7.04 (d, *J* = 5.6 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 5.42-5.38 (m, 1H), 4.96-4.75 (m, 1H), 3.73 (s, 3H), 2.16-2.12 (m, 1H), 1.58-1.51 (m, 1H), 1.12-1.06 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 2.36 min, *m/z* (M+H)⁺ = 500.2. HPLC (Method 5) *t*_R = 9.59 min.

[00309] **15B**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 10.38 (s, 1H), 8.55 (s, 1H), 8.52-8.50 (m, 2H), 8.12 (s, 1H), 7.69 (s, 1H), 7.01 (d, *J* = 5.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 5.42-5.38 (m, 1H), 4.96-4.76 (m, 1H), 3.72 (s, 3H), 2.17-2.10 (m, 1H), 1.57-1.49 (m, 1H), 1.13-1.05 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 2.34 min, *m/z* (M+H)⁺ = 500.2. HPLC (Method 5) *t*_R = 11.56 min.

Example 16



Step 1. 4-Methoxy-5-(methoxymethyl)pyrazolo[1,5-a]pyridine (16a)

[00310] To a solution of **7a** (200 mg, 1.12 mmol) in THF (2 mL) was added NaH (67 mg, 1.68 mmol, 60% purity in mineral oil) at 0 °C, then the mixture was stirred at 0 °C for 30 min. Iodomethane (191 mg, 1.35 mmol) was added into the mixture and stirred at r.t. for 5 h. The mixture was diluted with H₂O (30 mL), extracted with EtOAc (15 mL*3), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to get compound **16a** (181 mg, 84% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 2.08 min, m/z (M+H)⁺ = 193.1.

Step 2. 4-Methoxy-5-(methoxymethyl)-3-nitropyrazolo[1,5-a]pyridine (16b)

[00311] To a solution of **16a** (180 mg, 0.94 mmol) in TFA (2 mL) was added KNO₃ (95 mg, 0.94 mmol) at 0 °C, then the mixture was stirred at r.t. for 4 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (10 mL*3). The combined organic layer was washed with *aq.* Na₂CO₃ and brine, dried over Na₂SO₄ and concentrated to get compound **16b** (150 mg, 67% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 2.16 min, m/z (M+H)⁺ = 238.1.

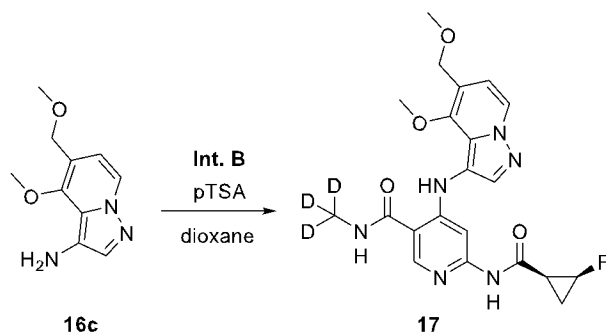
Step 3. 4-Methoxy-5-(methoxymethyl)pyrazolo[1,5-a]pyridin-3-amine (16c)

[00312] To a solution of **16b** (150 mg, 0.63 mmol) in EtOH (3 mL) and H₂O (1 mL) was added Fe powder (177 mg, 3.16 mmol) and NH₄Cl (169 mg, 3.16 mmol). Then the mixture was stirred at 80 °C for 2 h. The mixture was filtered and the filter cake was washed with EtOAc (10 mL). The filtrate was concentrated and diluted with H₂O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na₂SO₄, concentrated and purified by flash chromatography (DCM/MeOH = 50/1 to 5/1) to get compound **16c** (75 mg, 57% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 0.44 min, m/z (M+H)⁺ = 208.1.

Step 4. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(methoxymethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (16)

[00313] A mixture of **16c** (20 mg, 0.96 mmol), **Int. A** (25 mg, 0.096 mmol) and pTSA (17 mg, 0.096 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **16** (11.4 mg, 28% yield) as a pale-yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.34 (s, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 8.16 (d, *J* = 6.8 Hz, 1H), 8.05 (s, 1H), 7.87 (s, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.39 (s, 1H), 4.51 (s, 2H), 3.80 (s, 3H), 3.39 (s, 3H), 1.52-1.47 (m, 1H), 1.05-1.01 (m, 2H), 0.89-82 (m, 2H). LC-MS (ESI, Method 4) *t*_R = 1.72 min, *m/z* (M+H)⁺ = 428.4.

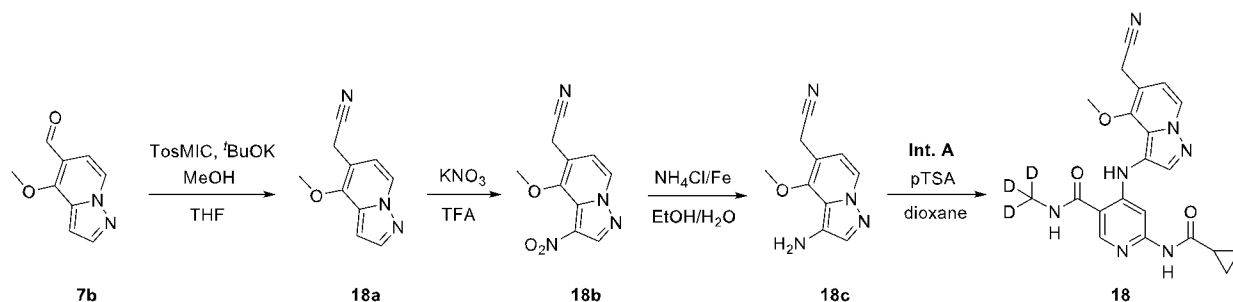
Example 17



Step 1. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(methoxymethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (17)

[00314] A mixture of **16c** (15 mg, 0.72 mmol), **Int. B** (16 mg, 0.058 mmol) and pTSA (12 mg, 0.072 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. Then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **17** (10.7 mg, 33% yield) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 10.33 (s, 1H), 8.51 (s, 1H), 8.46 (s, 1H), 8.39 (d, *J* = 6.8 Hz, 1H), 8.03 (s, 1H), 7.64 (s, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 4.92-4.72 (m, 1H), 4.41 (s, 2H), 3.67 (s, 3H), 3.26 (s, 3H), 2.11-2.08 (m, 1H), 1.55-1.45 (m, 1H), 1.08-1.03 (m, 1H). LC-MS (ESI, Method 4) *t*_R = 1.68 min, *m/z* (M+H)⁺ = 446.3.

Example 18



Step 1. 2-(4-Methoxypyrazolo[1,5-a]pyridin-5-yl)acetonitrile (18a)

[00315] To a suspension of *t*-BuOK (127 mg, 1.14 mmol) in THF (2 mL) was added TosMIC (111 mg, 0.57 mmol) in THF (2 mL) at -60 °C, then the mixture was stirred at -60 °C for 15 min. A solution of **7b** (50 mg, 0.28 mmol) in THF (1 mL) was added into the mixture dropwise at -60 °C and stirred for another 1.5 h at -60 °C. MeOH (5 mL) was added into the mixture and the mixture was stirred at 70 °C for 20 min. The mixture was then concentrated and diluted with H₂O (20 mL), extracted with EtOAc (10 mL*3), wash with brine (15 mL), dried over Na₂SO₄, concentrated and purified by flash chromatography (PE/EA = 10/1 to 1/2) to get compound **18a** (10 mg, 19 % yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 1.82 min, *m/z* (M+H)⁺ = 188.1.

Step 2. 2-(4-Methoxy-3-nitropyrazolo[1,5-a]pyridin-5-yl)acetonitrile (18b)

[00316] To a solution of **18a** (10 mg, 0.053 mmol) in TFA (1 mL) was added KNO₃ (5 mg, 0.053 mmol) at 0 °C, then the mixture was stirred at r.t. for 4 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (10 mL*3). The combined organic layer was washed with *aq.* Na₂CO₃ and brine, dried over Na₂SO₄, concentrated to get compound **18b** (10 mg, 81% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 1.94 min, *m/z* (M+H)⁺ = 233.1.

Step 3. 2-(3-Amino-4-methoxypyrazolo[1,5-a]pyridin-5-yl)acetonitrile (18c)

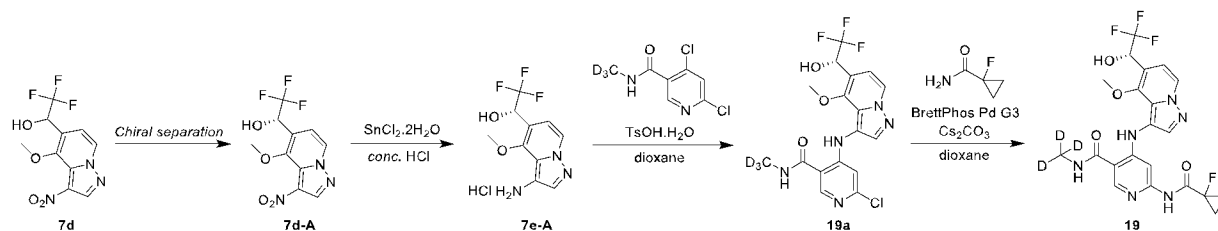
[00317] To a solution of **18b** (10 mg, 0.043 mmol) in EtOH (1 mL) and H₂O (0.2 mL) was added Fe powder (12 mg, 0.22 mmol) and NH₄Cl (12 mg, 0.22 mmol). Then the mixture was stirred at 80 °C for 2 h. The mixture was filtered and the filter cake was washed with EtOAc (10 mL). The filtrate was concentrated and diluted with H₂O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na₂SO₄, concentrated to get compound **18c** (5

mg, 57% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 0.45$ min, m/z (M+H)⁺ = 203.2.

Step 4. 4-((5-(Cyanomethyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)nicotinamide (18)

[00318] A solution of **18c** (5 mg, 0.025 mmol), **Int. A** (6 mg, 0.025 mmol) and pTSA (4 mg, 0.025 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 2 h. Then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **18** (2 mg, 19% yield) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.64 (s, 1H), 10.31 (s, 1H), 8.51 (s, 1H), 8.48-8.46 (m, 2H), 8.06 (s, 1H), 7.62 (s, 1H), 6.83 (d, $J = 7.2$ Hz, 1H), 3.98 (s, 2H), 3.70 (s, 3H), 1.93-1.87 (m, 1H), 0.70-0.68 (m, 4H). LC-MS (ESI, Method 4) $t_R = 1.48$ min, m/z (M+H)⁺ = 423.3.

Example 19



Step 1. (S)-2,2,2-trifluoro-1-(4-methoxy-3-nitropyrazolo[1,5-*a*]pyridin-5-yl)ethan-1-ol (7d-A)

[00319] **7d** (5.9 g, 20 mmol) was separated by chiral *prep*-HPLC (Method G) to afford **7d-A** (2.6 g, 44% yield) as a green solid.

[00320] ¹H NMR (400 MHz, CDCl₃) δ 8.68 (s, 1H), 8.42 (d, $J = 6.8$ Hz, 1H), 7.33 (d, $J = 6.8$ Hz, 1H), 5.70-7.67 (m, 1H), 3.92 (s, 3H). HPLC (Method 8) $t_R = 6.06$ min.

Step 2. (S)-1-(3-amino-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethan-1-ol hydrochloride (7e-A)

[00321] To a mixture of **7d-A** (1.1 g, 3.78 mmol) in *conc.* HCl (15 mL) was added SnCl₂·2H₂O (1.7 g, 7.56 mmol) at 0 °C. After stirring at 10 °C for 1 h, the reaction mixture was filtered. The filter cake was dried under vacuum to afford **7e-A** (1 g, 89% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 0.81$ min, m/z (M+H)⁺ = 262.0.

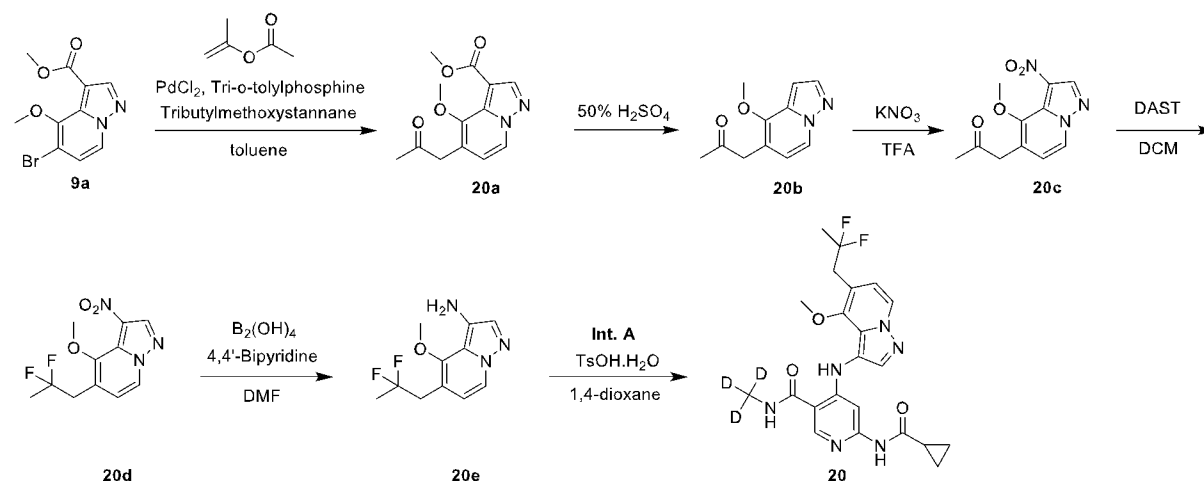
Step 3. (S)-6-chloro-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)nicotinamide (19a)

[00322] A mixture of **7e-A** (55 mg, 0.21 mmol), 4,6-dichloro-*N*-(methyl-*d*₃)nicotinamide (48 mg, 0.23 mmol) and TsOH.H₂O (16 mg, 0.084 mmol) in 1,4-dioxane (0.3 mL) was stirred at 100 °C for 18 h. After cooling to r.t., the mixture was concentrated. And the residue was purified by flash chromatography on silica gel (DCM/MeOH = 19/1) to afford **19a** (50 mg, 55% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.16 min, *m/z* (M+H)⁺ = 433.0.

Step 4. (S)-6-(1-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)nicotinamide (19)

[00323] A mixture of **19a** (50.0 mg, 0.12 mmol), 1-fluorocyclopropane-1-carboxamide (60.0 mg, 0.58 mmol), Cs₂CO₃ (113 mg, 0.35 mmol) and Brettphos Pd G3 (21 mg, 0.023 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **19** (5.2 mg, 9% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.37 (s, 1H), 9.97 (s, 1H), 8.63 (s, 1H), 8.61-8.51 (m, 2H), 8.15 (s, 1H), 7.61 (s, 1H), 7.03 (d, *J* = 4.4 Hz, 1H), 6.91 (d, *J* = 6.4 Hz, 1H), 5.43-5.38 (m, 1H), 3.73 (s, 3H), 1.47-1.35 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 2.48 min, *m/z* (M+H)⁺ = 500.1.

Example 20



Step 1. Methyl 4-methoxy-5-(2-oxopropyl)pyrazolo[1,5-a]pyridine-3-carboxylate (20a)

[00324] A mixture of **9a** (500 mg, 1.7 mmol), prop-1-en-2-yl acetate (263 mg, 2.6 mmol), tri-

o-tolylphosphine (32 mg, 0.105 mmol), tributylmethoxystannane (844 mg, 2.6 mmol) in toluene (5 mL) was stirred at 100 °C for 15 min. To the mixture was added PdCl₂ (9 mg, 0.052 mmol) and stirred at 100 °C for 3 h. The mixture was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford compound **20a** (130 mg, 28% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (d, *J* = 7.2 Hz, 1H), 8.42 (s, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 3.96 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 2.24 (s, 3H). LC-MS (ESI, Method 3) *t*_R = 1.36 min, *m/z* (M+H)⁺ = 263.1.

Step 2. 1-(4-Methoxypyrazolo[1,5-*a*]pyridin-5-yl)propan-2-one (20b)

[00325] A mixture of **20a** (270 mg, 1 mmol) in 50% H₂SO₄ (3 mL) was stirred at 85 °C for 4 h. After cooling down, the reaction mixture was diluted with ice-water (5 mL), basified with 1 *N* NaOH to pH = 3. The mixture was extracted with EtOAc (5 mL*3). The organic layer was washed with brine (5 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **20b** (200 mg, 95% yield) as a yellow oil. LC-MS (ESI, Method 3) *t*_R = 1.29 min, *m/z* (M+H)⁺ = 205.2.

Step 3. 1-(4-Methoxy-3-nitropyrzolo[1,5-*a*]pyridin-5-yl)propan-2-one (20c)

[00326] To a solution of **20b** (200 mg, 0.98 mmol) in TFA (2 mL) was added KNO₃ (99 mg, 0.98 mmol) at 0 °C. The mixture was stirred at 30 °C for 2 h. The solvent was removed by pumping through N₂. The residue was dissolved in EtOAc (15 mL) and basified with *sat.* Na₂CO₃ to pH = 9. The mixture was extracted with EtOAc (20 mL*2). The combined organic phase was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **20c** (153 mg, 62% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.34 min, *m/z* (M+H)⁺ = 250.1.

Step 4. 5-(2,2-Difluoropropyl)-4-methoxy-3-nitropyrzolo[1,5-*a*]pyridine (20d)

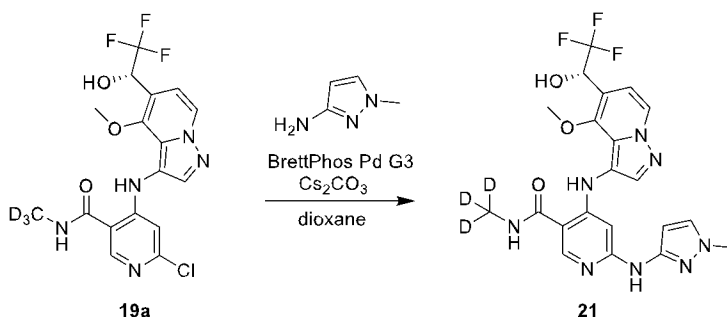
[00327] To a solution of **20c** (110 mg, 0.44 mmol) in DCM (2 mL) was added DAST (355 mg, 2 mmol) at 0 °C. Then the mixture was stirred at 25 °C for 10 h. The mixture was diluted with DCM (5 mL), washed with *sat.* NaHCO₃ (5 mL). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **20d** (84 mg, 70% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.55 min, *m/z* (M+H)⁺ = 272.2.

Step 5. 5-(2,2-Difluoropropyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-amine (20e)

[00328] To a solution of **20d** (74 mg, 0.27 mmol), 4,4'-Bipyridine (2 mg, 0.013 mmol) in DMF (1 mL) was added tetrahydroxydiboron (73 mg, 0.82 mmol) at 0 °C. After stirred at 10 °C for 10 min, the mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **20e** (50 mg, 75% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.42 min, m/z (M+H)⁺ = 242.2.

Step 6. 6-(Cyclopropanecarboxamido)-4-((5-(2,2-difluoropropyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (20)

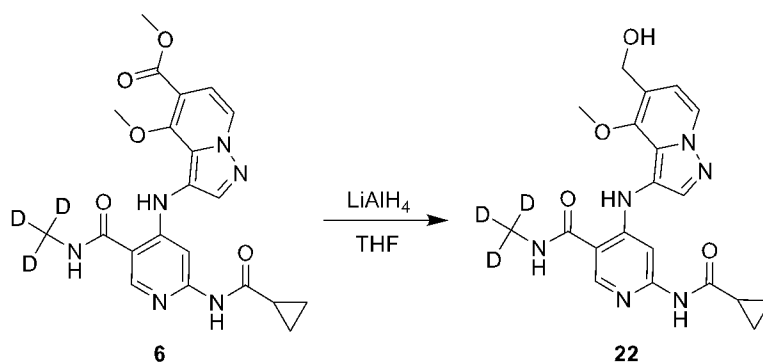
[00329] A mixture of **20e** (40 mg, 0.16 mmol), **Int. A** (46 mg, 0.18 mmol), TsOH.H₂O (15 mg, 0.08 mmol) in 1,4-dioxane (1 mL) was stirred at 90 °C for 7 h. The mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **20** (63 mg, 82% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 10.31 (s, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.43 (d, J = 7.2 Hz, 1H), 8.05 (s, 1H), 7.65 (s, 1H), 6.76 (d, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.26 (t, J = 16.4 Hz, 2H), 1.94-1.91 (m, 1H), 1.61 (t, J = 18.8 Hz, 3H), 0.73-0.70 (m, 4H). LC-MS (ESI, Method 2) t_R = 2.94 min, m/z (M+H)⁺ = 462.1.

Example 21**Step 1. (S)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)-6-((1-methyl-1*H*-pyrazol-3-yl)amino)nicotinamide (21)**

[00330] A mixture of **19a** (44 mg, 0.10 mmol), 1-methyl-1*H*-pyrazol-3-amine (49 mg, 0.51 mmol), Cs₂CO₃ (66 mg, 0.20 mmol) and Brettphos Pd G3 (18 mg, 0.02 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **21** (23 mg, 47% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 9.14 (s, 1H), 8.51 (d, J =

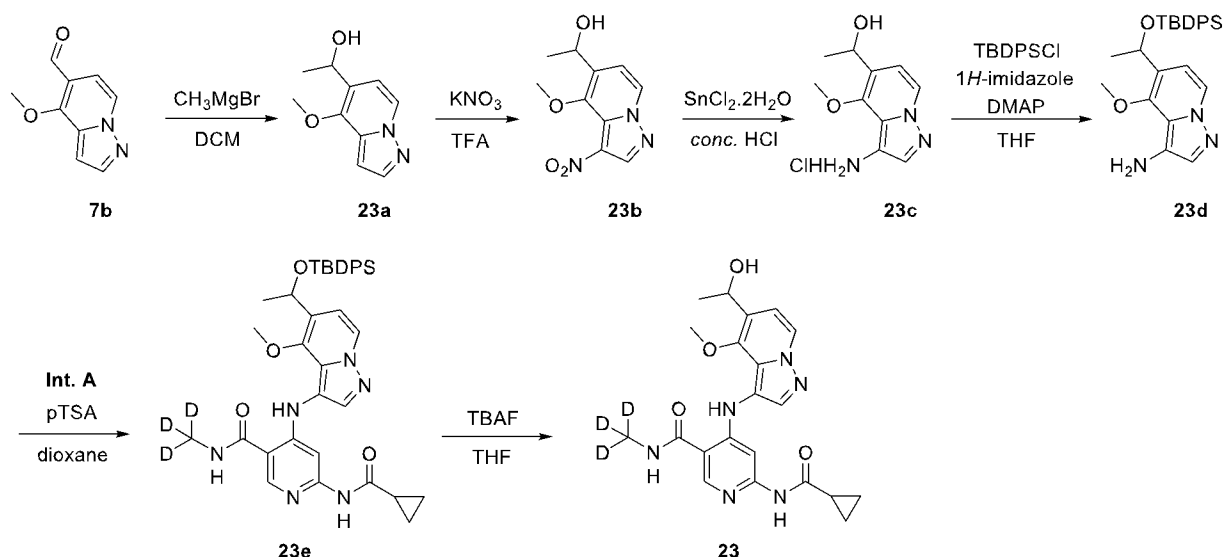
7.2 Hz, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.45 (s, 1H), 7.03-7.01 (m, 2H), 6.89 (d, J = 6.8 Hz, 1H), 6.08 (s, 1H), 5.44-5.39 (m, 1H), 3.77 (s, 3H), 3.63 (s, 3H). LC-MS (ESI, Method 2) t_R = 0.94 min, m/z ($M+H$)⁺ = 494.1.

Example 22



Step 1. 6-(Cyclopropanecarboxamido)-4-((5-(hydroxymethyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (22)

[00331] To a solution of **6** (110 mg, 0.25 mmol) in THF (5 mL) was slowly added LiAlH₄ (51 mg, 1.50 mmol) at 0 °C and the mixture was stirred at 0 °C for 2 h. The mixture was quenched with H₂O (0.05 mL), 15% *aq.* NaOH (0.05 mL) and H₂O (0.1 mL) at 0 °C sequentially. Then the mixture was stirred at r.t. for 15 min, dried over Na₂SO₄ and filtered. The filtrate was concentrated and purified by flash chromatography on silica gel (DCM/MeOH = 8/1) to afford **22** (70 mg, 68% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 11.31 (s, 1H), 8.50 (s, 1H), 8.48 (s, 1H), 8.42 (d, J = 7.2 Hz, 1H), 8.02 (s, 1H), 7.66 (s, 1H), 6.91 (d, J = 7.2 Hz, 1H), 5.29-5.26 (m, 1H), 4.53 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 1.97-1.91 (m, 1H), 0.73-0.72 (m, 4H). LC-MS (ESI, Method 2) t_R = 2.73 min, m/z ($M+H$)⁺ = 414.0.

Example 23**Step 1. 1-(4-Methoxypyrazolo[1,5-a]pyridin-5-yl)ethan-1-ol (23a)**

[00332] To a stirred solution of **7b** (755 mg, 4.29 mmol) in anhydrous DCM (10 mL) was added methylmagnesium bromide (2.89 mL, 8.67 mmol, 3 M in Et₂O) dropwise at 0 °C. Then the reaction mixture was stirred at 0 °C for 0.5 h. Then it was quenched with *sat.* NH₄Cl (5 mL) and extracted with DCM (10 mL*3). The combined organic layer was washed with water (15 mL), brine (10 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum and the residue was purified by flash chromatography (MeOH/DCM = 3/100) to afford compound **23a** (787 mg, 96% yield) as a light-yellow oil. LC-MS (ESI, Method 4) *t*_R = 1.49 min, *m/z* (M+H)⁺ = 193.1.

Step 2. 1-(4-Methoxy-3-nitropyrazolo[1,5-a]pyridin-5-yl)ethan-1-ol (23b)

[00333] To a stirred solution of **23a** (740 mg, 3.85 mmol) in TFA (7 mL) was added KNO₃ (385 mg, 3.77 mmol) at 0 °C. Then it was stirred at 25 °C for 0.5 h. The solvent was evaporated under reduced pressure to give a residue, which was purified by flash chromatography (PE/EA = 2/1) to give compound **23b** (830 mg, 91% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 1.75 min, *m/z* (M+H)⁺ = 238.0.

Step 3. 1-(3-Amino-4-methoxypyrazolo[1,5-a]pyridin-5-yl)ethan-1-ol hydrochloride (23c)

[00334] To a suspension of **23b** (830 mg, 3.50 mmol) in *conc.* HCl (10 mL) was added

SnCl₂·H₂O (3.28 g, 12.83 mmol) at 0 °C. Then it was stirred at 25 °C for 0.5 h. After filtration, the solid was dried under vacuum to give **23c** (802 mg, 94% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 0.34 min, *m/z* (M+H)⁺ = 208.2.

Step 4. 5-(1-((*Tert*-butyldiphenylsilyl)oxy)ethyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-amine (23d)

[00335] To a solution of **23c** (710 mg, 2.91 mmol), imidazole (992 mg, 14.57 mmol), DMAP (36 mg, 0.29 mmol) in THF (10 mL) was added *tert*-butylchlorodiphenylsilane (1.04 g, 3.79 mmol). Then the mixture was stirred at 50 °C for 2 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (15 mL*3), washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 10/1) to get compound **23d** (70 mg, 5.4% yield) as a yellow oil. LC-MS (ESI, Method 4) *t*_R = 4.10 min, *m/z* (M+H)⁺ = 446.3.

Step 5. 4-((5-(1-((*Tert*-butyldiphenylsilyl)oxy)ethyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-*d*₃)nicotinamide (23e)

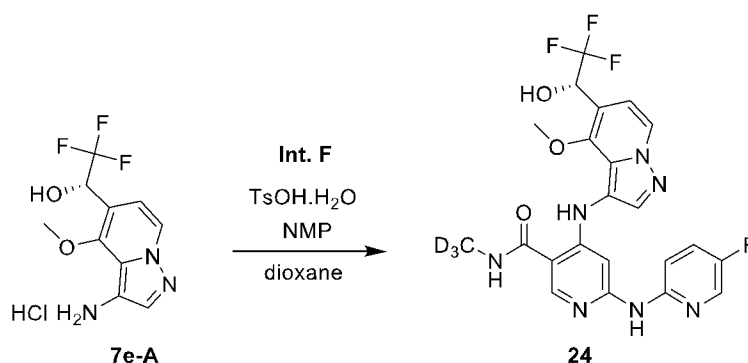
[00336] A mixture of **23d** (60 mg, 0.13 mmol), **Int. A** (21 mg, 0.081 mmol), pTSA (23 mg, 0.13 mmol) in dioxane (1 mL) was stirred at 70 °C for 6 h. The mixture was diluted with H₂O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 20/1) to get compound **23e** (20 mg, 22% yield) as a yellow oil. LC-MS (ESI, Method 4) *t*_R = 3.87 min, *m/z* (M+H)⁺ = 666.5.

Step 6. 6-(Cyclopropanecarboxamido)-4-((5-(1-hydroxyethyl)-4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (23)

[00337] Compound **23e** (20 mg, 0.03 mmol) was dissolved in TBAF solution (1 M in THF, 0.5 mL), then the mixture was stirred at r.t. for 2 h. The mixture was diluted with H₂O (10 mL), extracted with EtOAc (10 mL*3), washed with *aq.* NH₄Cl (10 mL) and brine (10 mL), dried over Na₂SO₄, concentrated and purified by flash chromatography (DCM/MeOH = 50/1 to 10/1) to get the crude product. Then the crude was purified by *prep*-HPLC (Method E) to get compound **23** (4.0 mg, 35% yield) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 10.29 (s, 1H), 8.52 (s, 1H), 8.48 (s, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 8.02 (s, 1H), 7.66 (s, 1H), 6.93

(d, $J = 7.2$ Hz, 1H), 5.26 (d, $J = 4.4$ Hz, 1H), 5.10-5.04 (m, 1H), 3.68 (s, 3H), 1.96-1.90 (m, 1H), 1.31 (d, $J = 6.4$ Hz, 3H), 0.74-0.71 (m, 4H). LC-MS (ESI, Method 4) $t_R = 1.00$ min, m/z (M+H)⁺ = 428.3.

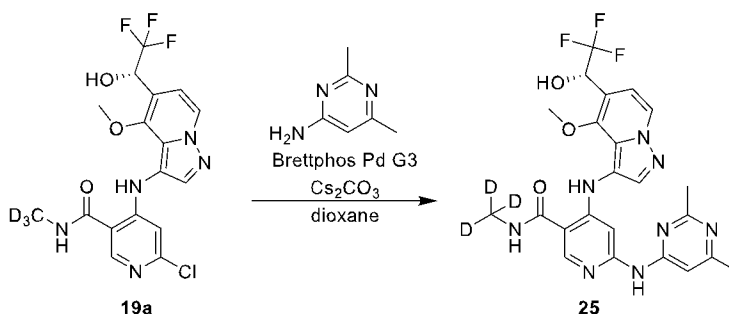
Example 24



Step 1. (S)-6-((5-fluoropyridin-2-yl)amino)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)nicotinamide (**24**)

[00338] A mixture of **7e-A** (35 mg, 0.12 mmol), **Int. F** (33 mg, 0.12 mmol) and TsOH.H₂O (2 mg, 0.012 mmol) in NMP (0.1 mL) and 1,4-dioxane (0.3 mL) was stirred at 100 °C for 12 h. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford **24** (14 mg, 23% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.34 (s, 1H), 9.64 (s, 1H), 8.52 (d, $J = 7.2$ Hz, 1H), 8.47-8.44 (m, 2H), 8.20 (s, 1H), 8.00 (s, 1H), 7.82-7.79 (m, 1H), 7.62-7.58 (m, 1H), 7.17 (s, 1H), 7.04 (d, $J = 5.2$ Hz, 1H), 6.91 (d, $J = 7.2$ Hz, 1H), 5.43-5.39 (m, 1H), 3.77 (s, 3H). LC-MS (ESI, Method 2) $t_R = 2.87$ min, m/z (M+H)⁺ = 509.0.

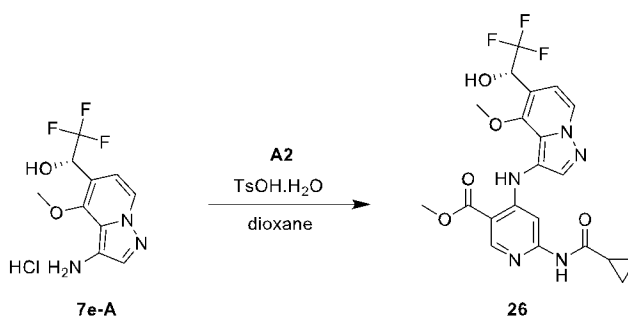
Example 25



Step 1. (S)-6-((2,6-Dimethylpyrimidin-4-yl)amino)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (25)

[00339] To a mixture of **19a** (50 mg, 0.11 mmol) and 2,6-dimethylpyrimidin-4-amine (28 mg, 0.23 mmol) in dioxane (2 mL) was added BrettPhos Pd G3 (41 mg, 0.05 mmol) and Cs₂CO₃ (75 mg, 0.23 mmol). The mixture was stirred at 100 °C for 3 h under N₂ atmosphere. The mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **25** (7.3 mg, 12% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 9.90 (s, 1H), 8.54-8.49 (m, 3H), 8.24 (s, 1H), 7.73 (s, 1H), 7.06-7.02 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 1H), 5.42-5.39 (m, 1H), 3.76 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H). LC-MS (ESI, Method 2) *t*_R = 0.88 min, *m/z* (M+H)⁺ = 520.2.

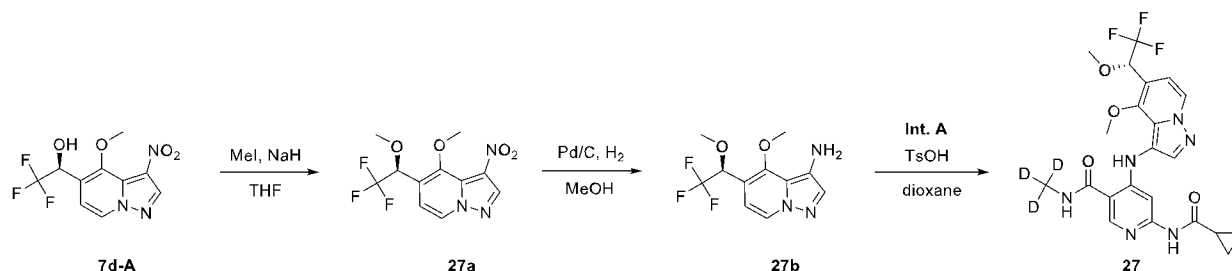
Example 26



Step 1. Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)nicotinate (26)

[00340] A mixture of **7e-A** (30 mg, 0.10 mmol), **A2** (23 mg, 0.090 mmol) and TsOH.H₂O (7.0 mg, 0.036 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 18 h. The mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **26** (12.2 mg, 25% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.82 (s, 1H), δ 9.57 (s, 1H), 8.67 (s, 1H), 8.54 (d, *J* = 6.8 Hz, 1H), 8.15 (s, 1H), 7.66 (s, 1H), 7.04 (d, *J* = 4.4 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 5.46-5.33 (m, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 2.03-1.86 (m, 1H), 0.79-0.65 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 2.64 min, *m/z* (M+H)⁺ = 480.1.

Example 27



Step 1. (S)-4-methoxy-3-nitro-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-a]pyridine (27a)

[00341] To a solution of **7d-A** (100 mg, 0.34 mmol) in THF (5 mL) was added NaH (21 mg, 0.52 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 20 min, then CH₃I (73 mg, 0.52 mmol, 0.032 mL) was added slowly. The mixture was moved to room temperature and stirred for 4 h. The mixture was quenched with *sat.* NH₄Cl (20 mL) and extracted with EtOAc (30 mL*2). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (EA in PE is 25%) to give **27a** (52 mg, 49% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.69 (s, 1H), 8.42 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 5.23 (q, *J* = 6.4 Hz, 1H), 3.92 (s, 3H), 3.45 (s, 3H). LC-MS (ESI, Method 4) *t*_R = 2.94 min, *m/z* (M+H)⁺ = 306.1.

Step 2. (S)-4-methoxy-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-a]pyridin-3-amine (27b)

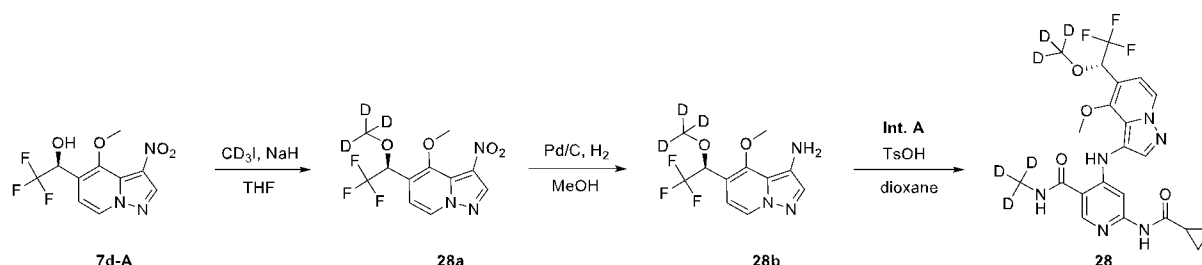
[00342] To a solution of **27a** (52 mg, 0.17 mmol) in MeOH (2 mL) was added Pd/C (5 mg, 0.05 mmol, 10% on charcoal) under H₂ atmosphere, the mixture was stirred at 25 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated to give **27b** (45 mg, 96% yield) as a brown solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) *t*_R = 1.92 min, *m/z* (M+H)⁺ = 276.1.

Step 3. (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)nicotinamide (27)

[00343] To a solution of **27b** (45 mg, 0.16 mmol) and **Int. A** (34 mg, 0.13 mmol) in dioxane (2 mL) was added TsOH (31 mg, 0.18 mmol). The mixture was stirred at 85 °C for 3 h. The

mixture was concentrated under vacuum and the residue was purified by *prep*-HPLC (Method E) to give **27** (18 mg, 22% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 10.37 (s, 1H), 8.53 (s, 1H), 8.49 (d, *J* = 7.2 Hz, 1H), 8.47 (s, 1H), 8.11 (s, 1H), 7.68 (s, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 3.30 (s, 3H), 1.97-1.82 (m, 1H), 0.73-0.61 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 2.29 min, *m/z* (M+H)⁺ = 496.4.

Example 28



Step 1. (*S*)-4-methoxy-3-nitro-5-(2,2,2-trifluoro-1-(methoxy-*d*₃)ethyl)pyrazolo[1,5-*a*]pyridine (**28a**)

[00344] To a solution of **7d-A** (100 mg, 0.34 mmol) in THF (5 mL) was added NaH (21 mg, 0.52 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 20 min, then CD₃I (75 mg, 0.52 mmol, 0.032 mL) was added slowly. The mixture was moved to room temperature and stirred for 4 h. The mixture was quenched with *sat.* NH₄Cl (20 mL) and extracted with EtOAc (30 mL*2). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (EA in PE is 25%) to give **28a** (55 mg, 52% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 2.91 min, *m/z* (M+H)⁺ = 309.1.

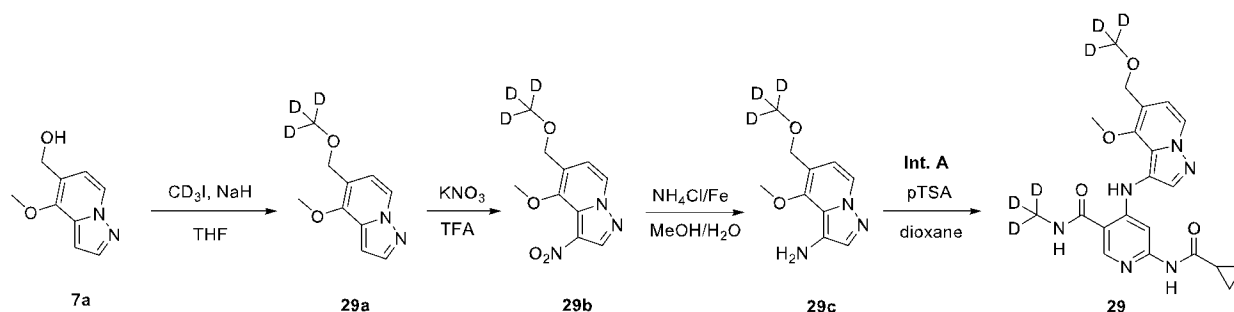
Step 2. (*S*)-4-methoxy-5-(2,2,2-trifluoro-1-(methoxy-*d*₃)ethyl)pyrazolo[1,5-*a*]pyridin-3-amine (**28b**)

[00345] To a solution of **28a** (55 mg, 0.17 mmol) in MeOH (2 mL) was added Pd/C (5 mg, 0.05 mmol, 10% on charcoal) under H₂ atmosphere. The mixture was stirred at 25 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated to give **28b** (45 mg, 91% yield) as a brown solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) *t*_R = 1.89 min, *m/z* (M+H)⁺ = 279.1.

Step 3. (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-(methoxy-*d*₃)ethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (28)

[00346] To a solution of **28b** (45 mg, 0.16 mmol) and **Int. A** (34 mg, 0.13 mmol) in dioxane (2 mL) was added TsOH (31 mg, 0.18 mmol), the mixture was stirred at 85 °C for 3 h. The mixture was concentrated under vacuum and the residue was purified by *prep*-HPLC (Method E) to give **28** (23 mg, 28% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 10.37 (s, 1H), 8.53 (s, 1H), 8.49 (d, *J* = 7.2 Hz, 1H), 8.47 (s, 1H), 8.11 (s, 1H), 7.68 (s, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 1.95-1.85 (m, 1H), 0.74-0.61 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 2.27 min, *m/z* (M+H)⁺ = 499.4.

Example 29



Step 1. 4-Methoxy-5-((methoxy-*d*₃)methyl)pyrazolo[1,5-*a*]pyridine (29a)

[00347] To a solution of **7a** (80 mg, 0.45 mmol) in THF (1 mL) was added NaH (23 mg, 0.58 mmol, 60% purity in mineral oil) at 0 °C, then the mixture was stirred at 0 °C for 30 min. Iodomethane-*d*₃ (78 mg, 0.54 mmol) was added into the mixture, then the mixture was stirred at r.t. for 1 h. The mixture was diluted with H₂O (30 mL), extracted with EtOAc (15 mL*3), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to get compound **29a** (80 mg, 91% yield) as a yellow oil. LC-MS (ESI, Method 4) *t*_R = 2.05 min, *m/z* (M+H)⁺ = 196.1.

Step 2. 4-Methoxy-5-((methoxy-*d*₃)methyl)-3-nitropyrazolo[1,5-*a*]pyridine (29b)

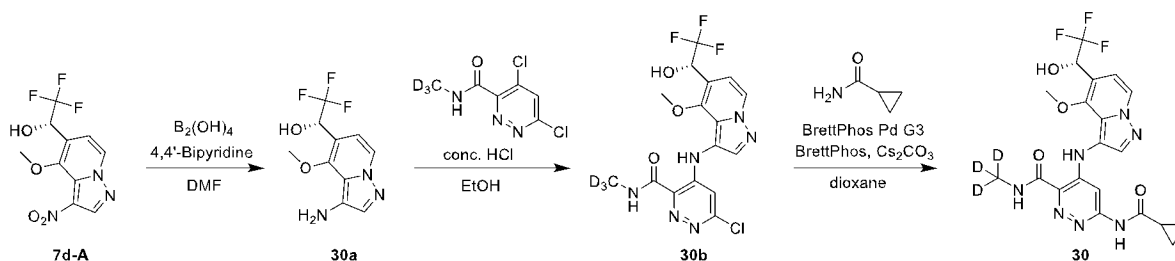
[00348] To a solution of **29a** (80 mg, 0.41 mmol) in TFA (1 mL) was added KNO₃ (41 mg, 0.41 mmol) at 0 °C, then the mixture was stirred at r.t. for 4 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (10 mL*3). The combined organic layer was washed with *aq.* Na₂CO₃ and *sat.* brine, dried over Na₂SO₄ and concentrated to get compound **29b** (90 mg, 91% yield) as a yellow oil. LC-MS (ESI, Method 4) *t*_R = 2.16 min, *m/z* (M+H)⁺ = 241.1.

Step 3. 4-Methoxy-5-((methoxy-*d*₃)methyl)pyrazolo[1,5-*a*]pyridin-3-amine (29c)

[00349] To a solution of **29b** (90 mg, 0.37 mmol) in MeOH (2 mL) and H₂O (0.5 mL) was added Fe powder (105 mg, 1.87 mmol) and NH₄Cl (100 mg, 1.87 mmol). Then the mixture was stirred at 70 °C for 2 h. The mixture was filtered and washed with EtOAc (10 mL). The filtrate was concentrated and diluted with H₂O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na₂SO₄, concentrated and purified by flash chromatography (DCM/MeOH = 50/1 to 5/1) to get compound **29c** (70 mg, 89% yield) as a yellow oil. LC-MS (ESI, Method 4) *t*_R = 0.45 min, *m/z* (M+H)⁺ = 211.3.

Step 4. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-((methoxy-*d*₃)methyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (29)

[00350] A mixture of **29c** (33 mg, 0.16 mmol), **Int. A** (40 mg, 0.16 mmol) and pTSA (27 mg, 0.16 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **29** (18.4 mg, 27% yield) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 10.34 (s, 1H), 8.52 (s, 1H), 8.48 (s, 1H), 8.42 (d, *J* = 7.2 Hz, 1H), 8.05 (s, 1H), 7.68 (s, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.44 (s, 2H), 3.70 (s, 3H), 1.96-1.90 (m, 1H), 0.74-0.71 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 1.68 min, *m/z* (M+H)⁺ = 431.4.

Example 30**Step 1. (*S*)-1-(3-amino-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethan-1-ol (30a)**

[00351] To a solution of **7d-A** (100 mg, 0.34 mmol), 4,4'-Bipyridine (2 mg, 0.013 mmol) in DMF (1 mL) was added tetrahydroxydiboron (92 mg, 1.032 mmol) at 0 °C. After stirred at 10 °C for 10 min, the mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **30a** (45 mg, 50% yield) as a green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.16 (d,

$J = 7.2$ Hz, 1H), 7.49 (s, 1H), 6.83 (d, $J = 6.0$ Hz, 1H), 6.58 (d, $J = 7.6$ Hz, 1H), 5.36-5.29 (m, 1H), 4.31 (s, 2H), 3.87 (3, 3H).

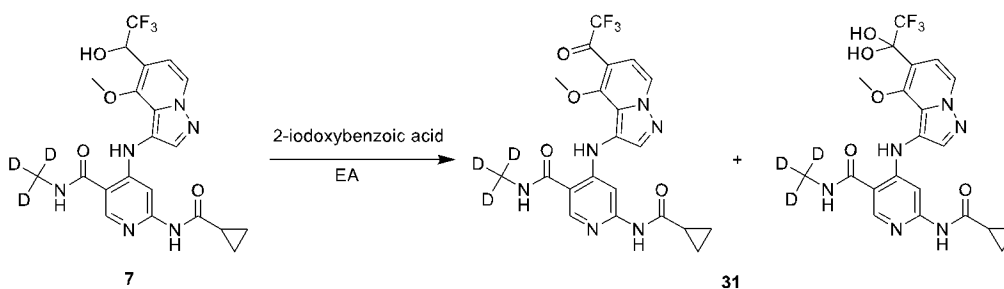
Step 2. (S)-6-chloro-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl- d_3)pyridazine-3-carboxamide (30b)

[00352] To a solution of **30a** (45 mg, 0.17 mmol) and 4,6-dichloro-*N*-(methyl- d_3)pyridazine-3-carboxamide (47 mg, 0.22 mmol) in EtOH (0.5 mL) was added *conc.* HCl (7 mg, 0.17 mmol) and stirred at 80 °C for 12 h. The reaction mixture was purified by *prep*-HPLC (Method A) to afford **30b** (60 mg, 80% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.14$ min, m/z (M+H)⁺ = 434.1.

Step 3. (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl- d_3)pyridazine-3-carboxamide (30)

[00353] A mixture of **30b** (60 mg, 0.14 mmol), cyclopropanecarboxamide (35 mg, 0.41 mmol), BrettPhos (15 mg, 0.03 mmol) and BrettPhos Pd G3 (25.08 mg, 0.03 mmol) in dioxane (0.5 mL) was stirred at 100 °C under N₂ for 12 h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to give compound **30** (15 mg, 22% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO- d_6) δ 11.24 (s, 1H), 10.55 (s, 1H), 9.09 (s, 1H), 8.54 (d, $J = 7.2$ Hz, 1H), 8.12 (s, 1H), 7.79 (s, 1H), 7.04 (d, $J = 5.6$ Hz, 1H), 6.93 (d, $J = 7.2$ Hz, 1H), 5.40-5.37 (m, 1H), 3.72 (s, 3H), 2.01-1.99 (m, 1H), 0.79-0.75 (m, 4H). LC-MS (ESI, Method 2) $t_R = 0.98$ min, m/z (M+H)⁺ = 483.1.

Example 31

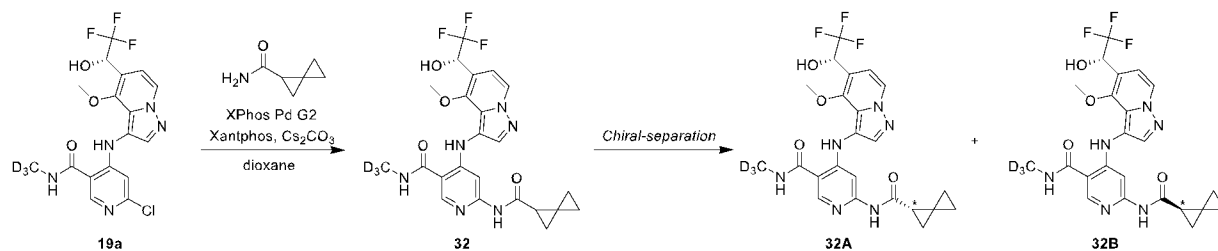


6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoroacetyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl- d_3)nicotinamide and 6-(Cyclopropanecarboxamido)-4-((4-

methoxy-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (31)

[00354] To a solution of **7** (50 mg, 0.10 mmol) in EtOAc (0.5 mL) was added 2-iodoxybenzoic acid (116 mg, 0.40 mmol). After stirring at 95 °C for 12 h, the reaction mixture was concentrated to dryness and purified by flash chromatography (DCM/MeOH = 10/1) to afford **31** as a brown solid as a mixture. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 0.2H), 10.79 (s, 0.2H), 10.69 (s, 0.8H), 10.37 (s, 0.8H), 8.62 (s, 0.2H), 8.56 (s, 0.2H), 8.55 (s, 0.8H), 8.54 (d, *J* = 8.0 Hz, 0.2H), 8.53 (s, 0.8H), 8.42 (d, *J* = 7.6 Hz, 0.8H), 8.28 (s, 0.2H), 8.10 (s, 0.8H), 7.93 (s, 0.2H), 7.75 (s, 0.8H), 7.71 (s, 1.6H), 7.04 (d, *J* = 7.2 Hz, 0.2H), 6.98 (d, *J* = 7.6 Hz, 0.8H), 3.90 (s, 0.6H), 3.70 (s, 2.4H), 1.97-1.93 (m, 1H), 0.77-0.73 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 1.99 min, *m/z* (M+H)⁺ = 480.2, 498.2.

Example 32



Step 1. 4-((4-Methoxy-5-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)-6-(spiro[2.2]pentane-1-carboxamido)nicotinamide (32)

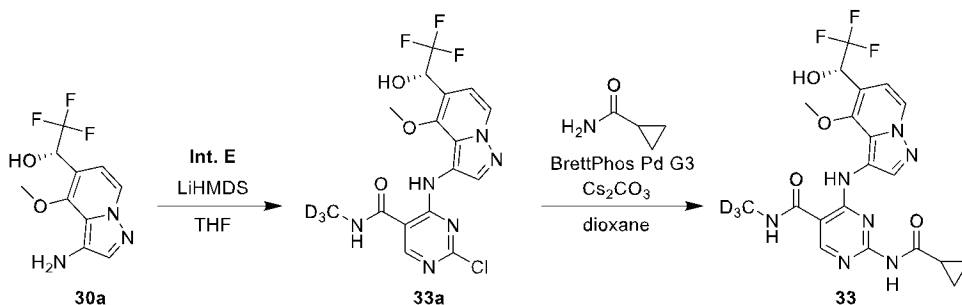
[00355] A mixture of **19a** (30.0 mg, 0.07 mmol) and spiro[2.2]pentane-1-carboxamide (39.0 mg, 0.35 mmol), Xantphos (8 mg, 0.014 mmol), XPhos Pd G2 (11 mg, 0.014 mmol) and Cs₂CO₃ (45 mg, 0.14 mmol) in 1,4-dioxane (0.4 mL) was stirred at 100 °C for 12 h under N₂ atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **32** (7 mg, 20% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.49 (s, 1H), 10.40 (d, *J* = 6.4 Hz, 1H), 8.56-8.49 (m, 3H), 8.14 (s, 1H), 7.74-7.71 (m, 1H), 7.04 (d, *J* = 5.6 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 5.42-5.39 (m, 1H), 3.72 (s, 3H), 2.31-2.28 (m, 1H), 1.35-1.30 (m, 1H), 1.26-1.23 (m, 1H), 0.85-0.79 (m, 3H), 0.68-0.67 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 1.11 min, *m/z* (M+H)⁺ = 508.0.

Step 2. 4-((4-Methoxy-5-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)-6-((*S*^{*})-spiro[2.2]pentane-1-carboxamido)nicotinamide (**32A**) and 4-((4-Methoxy-5-((*S*)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)-6-((*R*^{*})-spiro[2.2]pentane-1-carboxamido)nicotinamide (**32B**)

[00356] Compound **32** (23 mg, 0.05 mmol) was separated by chiral *prep*-HPLC (Method H) to obtain **32A** (5 mg, 22% yield) as a white solid and **32B** (6.5 mg, 28% yield) as a white solid. **32A**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.47 (s, 1H), 10.40 (s, 1H), 8.54-8.49 (m, 3H), 8.14 (s, 1H), 7.74 (s, 1H), 7.04 (d, *J* = 4.4 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 5.42-5.38 (m, 1H), 3.73 (s, 3H), 2.31-2.28 (m, 1H), 1.30-1.26 (m, 2H), 0.83-0.82 (m, 3H), 0.68-0.65 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 1.11 min, *m/z* (M+H)⁺ = 508.0. HPLC (Method 7) *t*_R = 8.14 min.

[00357] **32B**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.47 (s, 1H), 10.38 (s, 1H), 8.56-8.49 (m, 3H), 8.14 (s, 1H), 7.71 (s, 1H), 7.04 (d, *J* = 5.2 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 5.42-5.39 (m, 1H), 3.73 (s, 3H), 2.31-2.28 (m, 1H), 1.30-1.25 (m, 2H), 0.84-0.81 (m, 3H), 0.69-0.66 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 1.11 min, *m/z* (M+H)⁺ = 508.0. HPLC (Method 7) *t*_R = 10.48 min.

Example 33



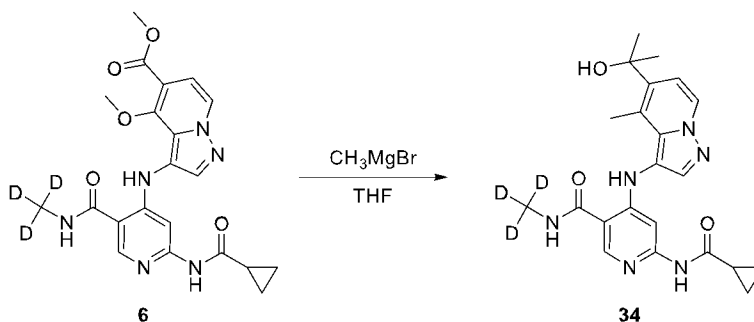
Step 1. (*S*)-2-chloro-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)pyrimidine-5-carboxamide (**33a**)

[00358] To a solution of **30a** (80 mg, 0.31 mmol) and **Int. E** (77 mg, 0.37 mmol) in THF (0.8 mL) was added LiHMDS (1.2 mL, 1.2 mmol, 1 M in THF) at -40 °C. The reaction was stirred at -40 °C to r.t. for 1 h and quenched with H₂O (2 mL). The organic solvent was removed under reduced pressure. The formed solid was collected by filtering and purified by flash chromatography (DCM/MeOH = 20/1) to afford **33a** (32 mg, 24% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.18 min, *m/z* (M+H)⁺ = 434.2.

Step 2. (S)-2-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)pyrimidine-5-carboxamide (33)

[00359] A mixture of **33a** (60 mg, 0.07 mmol), cyclopropanecarboxamide (31 mg, 0.37 mmol), BrettPhos Pd G3 (13 mg, 0.015 mmol) and Cs₂CO₃ (48 mg, 0.15 mmol) in dioxane (0.4 mL) was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **33** (8 mg, 22% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.73 (s, 1H), 10.96 (s, 1H), 9.61 (s, 1H), 8.74 (s, 1H), 8.63 (s, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 5.6 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 5.47-5.44 (m, 1H), 3.95 (s, 3H), 2.14-2.11 (m, 1H), 0.93-0.86 (m, 4H). LC-MS (ESI, Method 2) *t*_R = 1.11 min, *m/z* (M+H)⁺ = 483.0.

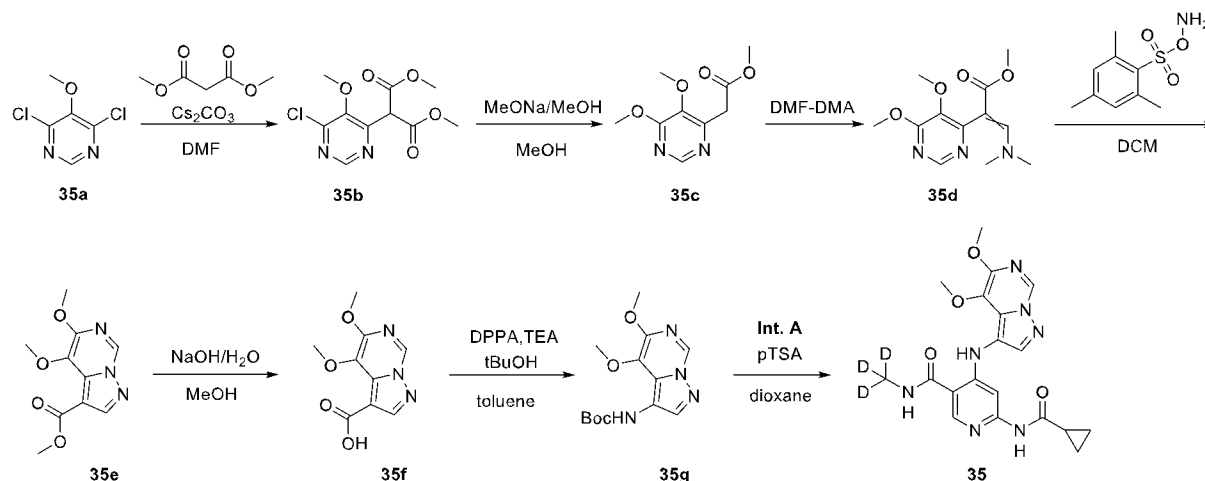
Example 34



Step 1. 6-(Cyclopropanecarboxamido)-4-((5-(2-hydroxypropan-2-yl)-4-methylpyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-*d*₃)nicotinamide (34)

[00360] To a solution of **6** (5 mg, 0.01 mmol) in THF (1 mL) was added CH₃MgBr (0.041 mL, 0.12 mmol, 3 M in Et₂O) slowly at 0 °C under N₂ atmosphere. The mixture was stirred for 10 min, then heated to 50 °C and stirred for 12 h. The mixture was quenched with *sat.* NH₄Cl (20mL) and extracted with DCM (20 mL*2). The combined organic layer was washed with brine (20 mL*2), dried and condensed by vacuum. The residue was purified by *prep*-HPLC (Method A) to give **34** (1.8 mg, 37% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.58 (s, 1H), 9.96 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 8.37 (d, *J* = 7.2 Hz, 1H), 7.87 (s, 1H), 7.24 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 5.14 (s, 1H), 2.55 (s, 3H), 1.91-1.82 (m, 1H), 1.47 (s, 6H), 0.69-0.59 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 1.46 min, *m/z* (M+H)⁺ = 426.3.

Example 35

**Step 1. Dimethyl 2-(6-chloro-5-methoxypyrimidin-4-yl)malonate (35b)**

[00361] To a solution of dimethyl malonate (7.38 g, 55.86 mmol, 6.36 mL) in DMF (100 mL) was added Cs_2CO_3 (36.40 g, 111.73 mmol) and 4,6-dichloro-5-methoxy-pyrimidine (10 g, 55.86 mmol), then the mixture was stirred at 100 °C for 2 h. The mixture was concentrated in vacuo, diluted with H_2O (100 mL), adjusted pH to 2 with 2 N HCl, extracted with EtOAc (100 mL*3), washed with brine (100 mL*2), dried over Na_2SO_4 , concentrated to get the crude compound **35b** (15 g, 98% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 2.23$ min, m/z ($\text{M}+\text{H}$) $^+ = 275.1$.

Step 2. Methyl 2-(5,6-dimethoxypyrimidin-4-yl)acetate (35c)

[00362] To a solution of **35b** (12 g, 43.69 mmol) in MeOH (50 mL) was added NaOMe (16.2 mL, 87.38 mmol, 5.4 M in MeOH), then the mixture was stirred at 60 °C for 2 h. The mixture was concentrated and diluted with H_2O (100 mL), adjusted pH to 2 with 2 N HCl, extracted with EtOAc (100 mL*3), washed with brine (100 mL), dried over Na_2SO_4 , concentrated and purified by flash chromatography (PE/EA = 20/1 to 1/1) to get compound **35c** (9 g, 97% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 1.79$ min, m/z ($\text{M}+\text{H}$) $^+ = 213.1$.

Step 3. Methyl 2-(5,6-dimethoxypyrimidin-4-yl)-3-(dimethylamino)acrylate (35d)

[00363] A solution of **35c** (1 g, 4.71 mmol) in DMF-DMA (1 mL) was stirred at 120 °C for 6 h. The mixture was concentrated to get compound **35d** (1.26 g, crude) as a yellow oil. LC-MS (ESI, Method 4) $t_R = 1.23$ min, m/z ($\text{M}+\text{H}$) $^+ = 268.1$.

Step 4. Methyl 4,5-dimethoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylate (35e)

[00364] To a solution of **35d** (1.26 g, 4.71 mmol) in DCM (10 mL) was added *O*-(mesitylsulfonyl)hydroxylamine (2.90 g, 9.43 mmol) at 0 °C, then the mixture was stirred at r.t. for 2 h. Then the mixture was concentrated and the solid was triturated with H₂O (10 mL), filtered, and the filter cake was washed with DCM (2 mL*2). The solid was dried in vacuo to get compound **35e** (600 mg, 54% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.42 (s, 1H), 8.45 (s, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H). LC-MS (ESI, Method 4) *t*_R = 2.04 min, *m/z* (M+H)⁺ = 238.1.

Step 5. 4,5-Dimethoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylic acid (35f)

[00365] To a suspension of **35e** (550 mg, 2.32 mmol) in MeOH (11 mL) was added a solution of NaOH (4.64 mL, 4.64 mmol, 1 M in H₂O) slowly, then the mixture was stirred at 40 °C for 16 h. The mixture was concentrated and then treated with H₂O (5 mL), adjusted pH to 1 with 2 N HCl. Then the mixture was filtered and the filter cake was washed with Et₂O (2 mL). The solid was dried in vacuo to get compound **35f** (90 mg, 17% yield) as a white solid. LC-MS (ESI, Method 4) *t*_R = 1.20 min, *m/z* (M+H)⁺ = 224.1.

Step 6. *Tert*-butyl (4,5-dimethoxypyrazolo[1,5-*c*]pyrimidin-3-yl)carbamate (35g)

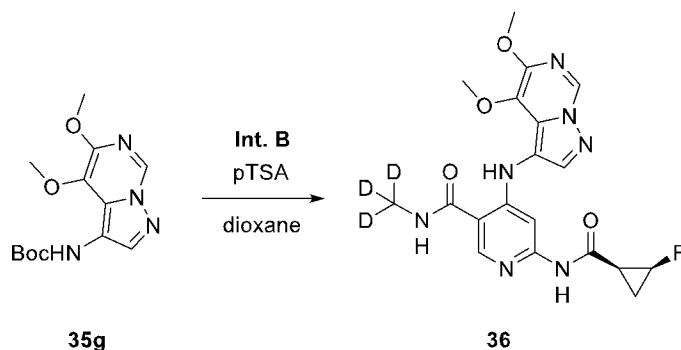
[00366] To a solution of **35f** (30 mg, 0.134 mmol) in toluene (1 mL) was added DPPA (74 mg, 0.27 mmol) and TEA (54 mg, 0.54 mmol), then the mixture was stirred at 80 °C for 1 h and cooled to r.t., then *t*BuOH (0.5 mL) was added into the mixture. The mixture was stirred at 110 °C for 4 h, concentrated and purified by flash chromatography (DCM/MeOH = 50/1 to 15/1) to get compound **35g** (25 mg, 63% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 2.64 min, *m/z* (M+H)⁺ = 295.2.

Step 7. 6-(Cyclopropanecarboxamido)-4-((4,5-dimethoxypyrazolo[1,5-*c*]pyrimidin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (35)

[00367] A mixture of **35g** (25 mg, 0.085 mmol), **Int. A** (22 mg, 0.085 mmol) and pTSA (15 mg, 0.085 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. Then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **35** (10.7 mg, 30% yield) as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 10.13 (s, 1H), 9.22 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 8.13 (s, 1H), 7.49 (s, 1H), 3.92 (s, 3H), 3.67 (s, 3H), 1.92-1.86

(m, 1H), 0.70-0.67 (m, 4H). LC-MS (ESI, Method 4) $t_R = 1.71$ min, m/z (M+H)⁺ = 415.3.

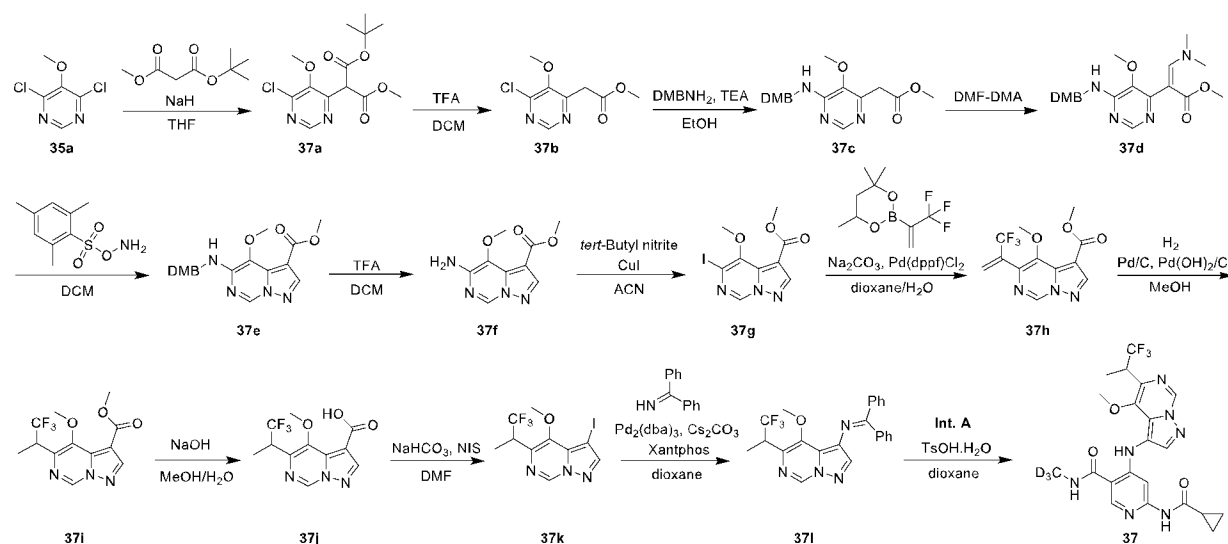
Example 36



Step 1. 4-((4,5-Dimethoxypyrazolo[1,5-c]pyrimidin-3-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d₃)nicotinamide (36)

[00368] A mixture of **35g** (18 mg, 0.061 mmol), **Int. B** (17 mg, 0.061 mmol) and pTSA (11 mg, 0.061 mmol) in dioxane (1 mL) was stirred at 100 °C for 2 h. Then the mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **36** (6.5 mg, 24% yield) as a pale-yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.00 (s, 1H), 8.79 (s, 1H), 8.25 (s, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.64 (s, 1H), 6.22 (s, 1H), 4.86-4.65 (m, 1H), 4.02 (s, 3H), 3.84 (s, 3H), 1.85-1.82 (m, 1H), 1.64-1.60 (m, 1H), 1.21-1.13 (m, 1H). LC-MS (ESI, Method 4) $t_R = 1.65$ min, m/z (M+H)⁺ = 433.3.

Example 37



Step 1. 1-*Tert*-butyl 3-methyl 2-(6-chloro-5-methoxypyrimidin-4-yl)malonate (37a)

[00369] To a solution of *tert*-butyl methyl malonate (13.08 g, 75.08 mmol) in THF (200 mL) was added NaH (6.01 g, 150.16 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then a solution of **35a** (11.2 g, 62.57 mmol) in THF (20 mL) was added to the mixture at 0 °C. The mixture was stirred at 80 °C for 3 h and poured into ice-water (150 mL). The mixture was acidified with 2 N HCl to pH = 2 and extracted with EtOAc (300 mL*2). The combined organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to afford **37a** (19.8 g, crude) as a yellow oil. LC-MS (ESI, Method 3) *t_R* = 1.26 min, *m/z* (M+H)⁺ = 261.2.

Step 2. Methyl 2-(6-chloro-5-methoxypyrimidin-4-yl)acetate (37b)

[00370] To a mixture of **37a** (18.0 g, 56.83 mmol) in DCM (150 mL) was added TFA (75 mL) at 0 °C. After stirring at r.t. for 4 h, the reaction mixture was concentrated. The residue was diluted with EtOAc (500 mL) and washed with *sat.* NaHCO₃ (150 mL) and brine (100 mL). The organic layer was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to afford **37b** (10.5 g, 85% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H), 3.95 (s, 3H), 3.91 (s, 2H), 3.75 (s, 3H).

Step 3. Methyl 2-(6-((2,4-dimethoxybenzyl)amino)-5-methoxypyrimidin-4-yl)acetate (37c)

[00371] A mixture of **37b** (1.0 g, 4.62 mmol), TEA (934 mg, 9.23 mmol) and DMBNH₂ (1.00 g, 6.00 mmol) in EtOH (10 mL) was stirred at 80 °C for 5 h. The mixture was diluted with H₂O (20 mL), extracted with EtOAc (40 mL*2). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to afford **37c** (1.33 g, 83% yield) as a white solid. LC-MS (ESI, Method 3) *t_R* = 1.07 min, *m/z* (M+H)⁺ = 348.2.

Step 4. (Z)-Methyl 2-(6-((2,4-dimethoxybenzyl)amino)-5-methoxypyrimidin-4-yl)-3-(dimethylamino)acrylate (37d)

[00372] A mixture of **37c** (1.33 g, 3.83 mmol) in DMF-DMA (10 mL) was stirred at 120 °C for 18 h. The mixture was concentrated to afford **37d** (1.54 g, crude) as a brown oil. LC-MS (ESI, Method 3) *t_R* = 1.07 min, *m/z* (M+H)⁺ = 403.3.

Step 5. Methyl 5-((2,4-dimethoxybenzyl)amino)-4-methoxypyrazolo[1,5-c]pyrimidine-3-carboxylate (37e)

[00373] To a mixture of **37d** (1.61 g, 4.00 mmol) in DCM (30 mL) was added dropwise a solution of *O*-(mesitylsulfonyl)hydroxylamine (1.03 g, 4.80 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. Another batch of a solution of *O*-(mesitylsulfonyl)hydroxylamine (515 mg, 2.40 mmol) in DCM (5 mL) was added into the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was concentrated and purified by flash chromatography on silica gel (DCM/MeOH = 50/1) to afford **37e** (788 mg, 53% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.84 (s, 1H), 8.27 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.41 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 5.64 (t, *J* = 6.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H).

Step 6. Methyl 5-amino-4-methoxypyrazolo[1,5-c]pyrimidine-3-carboxylate (37f)

[00374] To a mixture of **37e** (4.26 g, 11.44 mmol) in DCM (15 mL) was added TFA (15 mL) dropwise at r.t. The reaction mixture was stirred at r.t. for 1 h and concentrated under vacuum at 30 °C. The residue was dissolved in DCM (80 mL) and the solution was basified with 1 M NaOH to pH = 12. The mixture was extracted with DCM (80 mL). The organic layer was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to afford **37f** (1.94 g, 76% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.09 (s, 1H), 8.27 (s, 1H), 6.68 (brs, 2H), 3.77 (s, 3H), 3.71 (s, 3H).

Step 7. Methyl 5-iodo-4-methoxypyrazolo[1,5-c]pyrimidine-3-carboxylate (37g)

[00375] To a mixture of **37f** (1.1 g, 4.95 mmol) in ACN (12 mL) was added *tert*-Butyl nitrite (766 mg, 7.43 mmol, 0.88 mL) at 0 °C. The mixture was stirred at 15 °C for 10 min. CuI (1.41 g, 7.43 mmol) was added to the mixture and stirred at 70 °C for 2 h. After cooling to r.t., the reaction was quenched with 40 mL of 25% *aq.* NH₃·H₂O and extracted with EtOAc (60 mL*2). The combined organic layer was concentrated and the residue was purified by flash chromatography (PE/EA = 2/1) to afford **37g** (410 mg, 25% yield) as a yellow solid. LC-MS (ESI, Method 3) *t*_R = 1.24 min, *m/z* (M+H)⁺ = 333.9.

Step 8. Methyl 4-methoxy-5-(3,3,3-trifluoroprop-1-en-2-yl)pyrazolo[1,5-*c*]pyrimidine-3-carboxylate (37h)

[00376] A mixture of **37g** (450 mg, 1.35 mmol), 4,4,6-trimethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborinane (600 mg, 2.70 mmol), Na₂CO₃ (287 mg, 2.70 mmol) and Pd(dppf)Cl₂ (99 mg, 0.14 mmol) in 1,4-dioxane/H₂O (4.5 mL/1.5 mL) was stirred at 90 °C for 3 h. After cooled to r.t., the reaction mixture was diluted with EtOAc (15 mL), washed with water (7 mL) and brine (7mL). The organic layer was concentrated to afford **37h** (400 mg, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) *t*_R = 1.25 min, *m/z* (M+H)⁺ = 302.0.

Step 9. Methyl 4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidine-3-carboxylate (37i)

[00377] A mixture of **37h** (400 mg, 1.33 mmol), Pd(OH)₂/C (200 mg, Pd 20% on carbon, wetted with water) and Pd/C (200 mg, 10% wt. wetted with water) in MeOH (4 mL) was stirred at 50 °C under H₂ (50 psi) atmosphere for 18 h. The reaction mixture was filtered and the filtrate was concentrated to afford **37i** (400 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) *t*_R = 1.27 min, *m/z* (M+H)⁺ = 304.2.

Step 10. 4-Methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidine-3-carboxylic acid (37j)

[00378] A mixture of **37i** (400 mg, 1.32 mmol) and NaOH (106 mg, 2.64 mmol) in MeOH (8 mL) and H₂O (4 mL) was stirred at 40 °C for 10 h. The reaction mixture was concentrated and added into water (8 mL). The aqueous solution was acidified with 2 *N* HCl to pH = 1. The resultant mixture was extracted with EtOAc (20 mL*2) and the combined organic phase was concentrated. The residue was purified by *prep*-HPLC (Method A) to afford **37j** (180 mg, 51% yield) as a white solid. LC-MS (ESI, Method 3) *t*_R = 0.47 min, *m/z* (M+H)⁺ = 290.1.

Step 11. 3-Iodo-4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidine (37k)

[00379] To a mixture of **37j** (92 mg, 0.32 mmol) and NaHCO₃ (80 mg, 0.95 mmol) in DMF (2 mL) was added NIS (215 mg, 0.95 mmol) at 0 °C. The mixture was stirred at 40 °C for 10 h. After cooling to r.t., the reaction mixture was diluted with *sat.* Na₂S₂O₃ (5 mL) at 0 °C. Then the

mixture was extracted with EtOAc (8 mL*2). The combined organic layer was washed with brine (5 mL*2), dried over Na₂SO₄, filtered and the filtrate was concentrated to afford **37k** (115 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) $t_R = 1.38$ min, m/z (M+H)⁺ = 371.9.

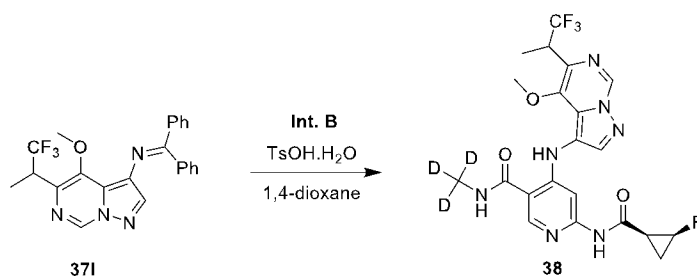
Step 12. *N*-(4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-3-yl)-1,1-diphenylmethanimine (37l)

[00380] A mixture of **37k** (115 mg, 0.31 mmol), diphenylmethanimine (112 mg, 0.62 mmol, 0.1 mL), Xantphos (18 mg, 0.031 mmol), Pd₂(dba)₃ (28 mg, 0.031 mmol) and Cs₂CO₃ (202 mg, 0.62 mmol) in 1,4-dioxane (1 mL) was stirred at 90 °C for 16 h under N₂. After cooling to r.t., the mixture was diluted with water (5 mL), extracted with EtOAc (8 mL*3). The combined organic layer was concentrated and the residue was purified by flash chromatography (PE/EA = 5/1) to afford **37l** (20 mg, 15% yield) as a yellow oil. LC-MS (ESI, Method 3) $t_R = 1.62$ min, m/z (M+H)⁺ = 425.2.

Step 13. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (37)

[00381] A mixture of **37l** (20 mg, 0.047 mmol), **Int. A** (12 mg, 0.047 mmol) and TsOH.H₂O (2 mg, 0.01 mmol) in 1,4-dioxane (0.5 mL) was stirred at 60 °C for 16 h. The mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **37** (7.2 mg, 32% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 10.36 (s, 1H), 9.37 (s, 1H), 8.56 (s, 1H), 8.52 (s, 1H), 8.33 (s, 1H), 7.63 (s, 1H), 4.20-4.03 (m, 1H), 3.74 (s, 3H), 2.02-1.87 (m, 1H), 1.45 (d, $J = 7.2$ Hz, 3H), 0.80-0.66 (m, 4H). LC-MS (ESI, Method 2) $t_R = 2.75$ min, m/z (M+H)⁺ = 481.2.

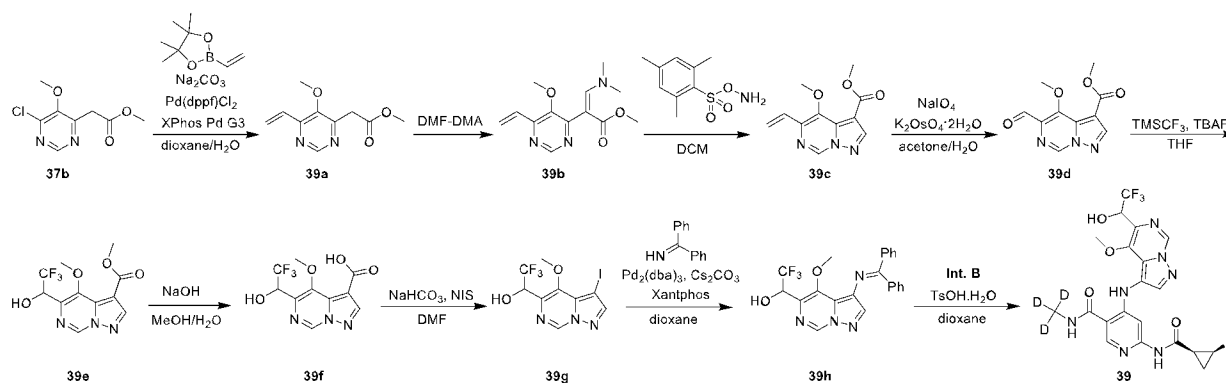
Example 38



Step 1. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (38)

[00382] A mixture of **37l** (20 mg, 0.047 mmol), **Int. B** (13 mg, 0.047 mmol) and TsOH.H₂O (3 mg, 0.016 mmol) in 1,4-dioxane (0.5 mL) was stirred at 80 °C for 8 h. After cooling to r.t., the mixture was diluted with EtOAc (6 mL), washed with water (2 mL) and brine (2 mL). The organic layer was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **38** (10.2 mg, 43% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.76 (s, 1H), 10.40-10.38 (m, 1H), 9.38 (s, 1H), 8.59 (s, 1H), 8.53 (s, 1H), 8.35 (s, 1H), 7.64-7.63 (m, 1H), 4.94-4.77 (m, 1H), 4.13-4.11 (m, 1H), 3.75-3.74 (m, 3H), 2.14-2.12 (m, 1H), 1.56-1.44 (m, 4H), 1.13-1.10 (m, 1H). LC-MS (ESI, Method 2) *t*_R = 2.73 min, *m/z* (M+H)⁺ = 499.2.

Example 39



Step 1. Methyl 2-(5-methoxy-6-vinylpyrimidin-4-yl)acetate (39a)

[00383] To a mixture of **37b** (12.1 g, 55.86 mmol) in dioxane (64 mL) and water (16 mL) was added Pd(dppf)Cl₂ (2.0 g, 2.79 mmol), XPhos Pd G3 (472 mg, 0.56 mmol) and Na₂CO₃ (11.8 g, 111.72 mmol). The reaction mixture was stirred at 90 °C for 28 h under N₂ atmosphere. After cooling to r.t., the mixture was diluted with water (20 mL) and extracted with EtOAc (70 mL*3). The organic layer was washed by brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **39a** (7 g, 60% yield) as a yellow oil. LC-MS (ESI, Method 3) *t*_R = 1.02 min, *m/z* (M+H)⁺ = 209.3.

Step 2. Methyl 3-(dimethylamino)-2-(5-methoxy-6-vinylpyrimidin-4-yl)acrylate (39b)

[00384] A mixture of **39a** (7 g, 33.61 mmol) in DMF-DMA (13.4 mL, 100.83 mmol) was stirred at 60 °C for 4 h. The mixture was concentrated to afford **39b** (8.7 g, crude) as a yellow

oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) $t_R = 0.94$ min, m/z $(M+H)^+ = 264.3$.

Step 3. Methyl 4-methoxy-5-vinylpyrazolo[1,5-*c*]pyrimidine-3-carboxylate (39c)

[00385] To a mixture **39b** (8.7 g, 33.04 mmol) in DCM (30 mL) was dropped a solution of amino 2,4,6-trimethylbenzenesulfonate (14.23 g, 66.09 mmol) in DCM (30 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h. The mixture was basified to pH = 9 with *sat.* Na₂CO₃. The separated aqueous layer was extracted with DCM (200 mL*3). The combined organic layer was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to afford **39c** (2.1 g, 27% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 1.17$ min, m/z $(M+H)^+ = 234.2$.

Step 4. Methyl 5-formyl-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylate (39d)

[00386] To a mixture **39c** (2.0 g, 8.58 mmol) in acetone (10 mL) was added K₂OsO₄·2H₂O (158 mg, 0.43 mmol). A solution of NaIO₄ (3.67 g, 17.15 mmol) in water (10 mL) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 1 h and filtered. The filtrate was concentrated and purified by flash chromatography on silica gel (PE/EA = 1/1) to afford **39d** (1.2 g, 59% yield) as a yellow solid. LC-MS (ESI, Method 3) $t_R = 0.94$ min, m/z $(M+H)^+ = 236.0$.

Step 5. Methyl 4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*c*]pyrimidine-3-carboxylate (39e)

[00387] To a mixture of **39d** (1.20 g, 5.10 mmol) in THF (10 mL) was added TMSCF₃ (1.60 g, 11.22 mmol) dropwise followed by TBAF (1.0 M in THF, 0.25 mL). After stirring at 0 °C for 10 min, the reaction mixture was diluted with THF (10 mL) and *aq.* HCl (10 mL, 1 M). The mixture was stirred at 25 °C for 1 h. The mixture was basified with *aq.* NaOH (1 M) to pH = 8 and extracted with EtOAc (50 mL*3). The combined organic layer was concentrated to afford **39e** (1 g, 64% yield) as a brown oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) $t_R = 1.12$ min, m/z $(M+H)^+ = 306.0$.

Step 6. 4-Methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*c*]pyrimidine-3-carboxylic acid (39f)

[00388] To a mixture of **39e** (600 mg, 1.97 mmol) in methanol (4 mL) and water (2 mL) was added NaOH (157.3 mg, 3.93 mmol) and the mixture was stirred at 45 °C for 8 h. The mixture

was adjusted with *aq.* HCl (2 M) to pH = 1 and extracted with EtOAc (20 mL*3). The organic layer was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **39f** (130 mg, 23% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 0.92 min, m/z (M+H)⁺ = 292.0.

Step 7. 2,2,2-Trifluoro-1-(3-iodo-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)ethan-1-ol (39g)

[00389] To a solution of **39f** (110 mg, 0.38 mmol) and NaHCO₃ (95 mg, 1.13 mmol) in DMF (1.2 mL) was added NIS (255 mg, 1.13 mmol) at 0 °C. The mixture was stirred at 15 °C for 18 h. The reaction was quenched with *sat.* Na₂S₂O₃ (10 mL) under ice-water bath, and extracted with EtOAc (15 mL*2). The combined organic layer was washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by *prep*-HPLC (Method A) to afford **39g** (16 mg, 11% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.19 min, m/z (M+H)⁺ = 373.9.

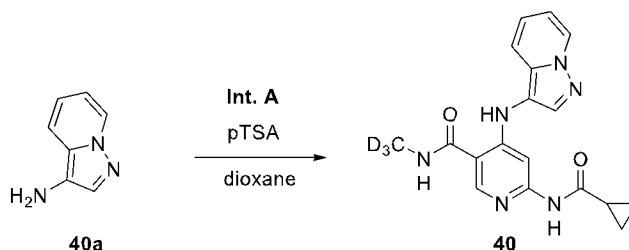
Step 8. 1-(3-((Diphenylmethylene)amino)-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)-2,2,2-trifluoroethan-1-ol (39h)

[00390] A mixture of **39g** (17 mg, 0.045 mmol), diphenylmethanimine (17 mg, 0.091 mmol), Xantphos (3 mg, 0.0046 mmol), Pd₂(dba)₃ (4 mg, 0.0046 mmol) and Cs₂CO₃ (30 mg, 0.091 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C for 8 h under N₂ atmosphere. The mixture was diluted with water (3 mL), extracted with EtOAc (5 mL*3). The combined organic layer was concentrated and the residue was purified by *prep*-TLC (PE/EA = 5/1) to afford **39h** (8 mg, 41% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.44 min, m/z (M+H)⁺ = 427.2.

Step 9. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*c*]pyrimidin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (39)

[00391] A mixture of **39h** (16 mg, 0.038 mmol), **Int. B** (12 mg, 0.045 mmol) and TsOH.H₂O (3 mg, 0.015 mmol) in 1,4-dioxane (0.5 mL) was stirred at 80 °C for 8 h. The mixture was filtered and washed with DCM (2 mL). The filter cake was purified by *prep*-TLC (DCM/MeOH = 10/1) to afford **39** (5.8 mg, 31% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 10.43 (s, 1H), 9.38 (s, 1H), 8.60 (s, 1H), 8.54 (s, 1H), 8.38 (s, 1H), 7.64 (s, 1H), 5.39-5.27 (m, 1H), 4.95-4.74 (m, 1H), 3.78 (s, 3H), 2.20-2.07 (m, 1H), 2.05-1.94 (m, 1H), 1.59-1.41 (m, 1H), 1.15-1.03 (m, 1H). LC-MS (ESI, Method 2) t_R = 2.45 min, m/z (M+H)⁺ = 501.0.

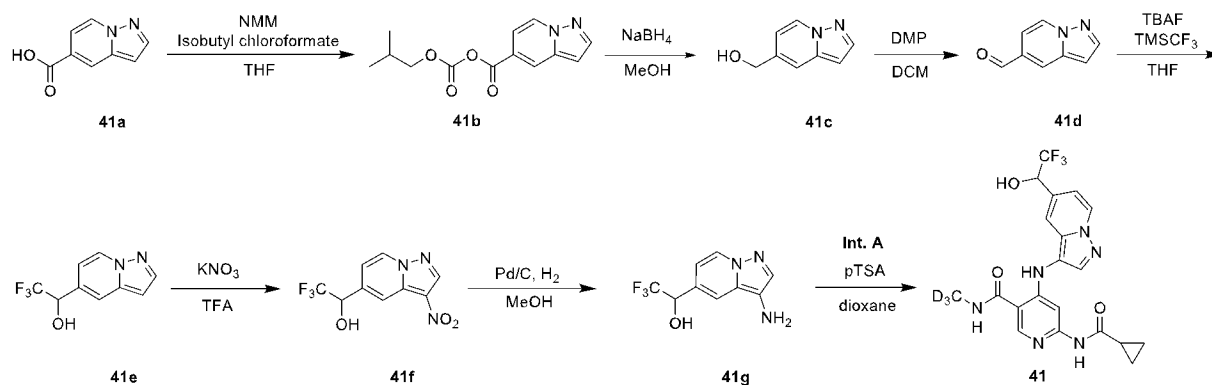
Example 40



Step 1. 6-(Cyclopropanecarboxamido)-*N*-(methyl-*d*₃)-4-(pyrazolo[1,5-*a*]pyridin-3-ylamino)nicotinamide (**40**)

[00392] To a solution of **Int. A** (20 mg, 0.078 mmol), pTSA (13 mg, 0.078 mmol) in dioxane (7 mL) was added **40a** (21 mg, 0.16 mmol) at r.t. The mixture was stirred at 100 °C for 3 h. It was added into H₂O (10 mL) and extracted by EA (20 mL). The combined organic layer was washed by brine (20 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by *prep*-HPLC (Method E) to afford **40** (16.5 mg, 60% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.63 (s, 1H), 10.06 (s, 1H), 8.68-8.65 (m, 1H), 8.54 (s, 1H), 8.49 (s, 1H), 8.04 (s, 1H), 7.42-7.39 (m, 1H), 7.38 (s, 1H), 7.23-7.18 (m, 1H), 6.95-6.90 (m, 1H), 1.95-1.86 (m, 1H), 0.72-0.63 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 4.44 min, *m/z* (M+H)⁺ = 354.3.

Example 41



Step 1. (Isobutyl carbonic) pyrazolo[1,5-*a*]pyridine-5-carboxylic anhydride (**41b**)

[00393] To a solution of **41a** (1 g, 6.17 mmol) in THF (20 mL) was added NMM (749 mg, 7.40 mmol) at 0 °C under nitrogen. Isobutyl chloroformate (1.01 g, 7.40 mmol) was dropped 5 minutes later. The reaction was stirred at 0 °C to r.t. for 2 h. The resulting solution was added

into H₂O (30 mL) and extracted by EA (50 mL). The combined organic layer was washed by brine (30 mL*2), dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo to afford **41b** (1.8 g, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) $t_R = 3.14$ min, m/z (M+H)⁺ = 263.1.

Step 2. Pyrazolo[1,5-*a*]pyridin-5-ylmethanol (41c)

[00394] To a solution of **41b** (1.8 g, crude) in methanol (20 mL) was added NaBH₄ (662 mg, 17.5 mmol) at 0 °C. The reaction was stirred at 0 °C for 2 h. The resulting solution was added into NH₄Cl solution (30 mL) and extracted by EA (40 mL). The combined organic layer was washed by brine (30 mL*2), dried over Na₂SO₄, filtered and concentrated in vacuo to afford **41c** (1 g, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) $t_R = 0.72$ min, m/z (M+H)⁺ = 149.1.

Step 3. Pyrazolo[1,5-*a*]pyridine-5-carbaldehyde (41d)

[00395] To a solution of **41c** (1 g, 5.40 mmol) in DCM (15 mL) was added Dess-Martin Periodinane (3.44 g, 8.10 mmol) at r.t. The reaction was stirred at 25 °C for 1 h. The resulting solution was filtered and the combined organic layer was concentrated in vacuo. The crude was purified by flash chromatography (EA in PE is 10-40%) to afford **41d** (600 mg, 76% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 1.34$ min, m/z (M+H)⁺ = 147.1.

Step 4. 2,2,2-Trifluoro-1-(pyrazolo[1,5-*a*]pyridin-5-yl)ethan-1-ol (41e)

[00396] To a solution of **41d** (300 mg, 2.05 mmol) and TMSCF₃ (409 mg, 2.87 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 107 mg, 0.41 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and at 25 °C for 12 h. Then 1 M HCl solution was added, and the reaction was stirred at 25 °C for 2 h. The mixture was adjusted to pH = 8 with *aq.* NaOH (1 M). The mixture was extracted with EA (15 mL*3). The organic layer was concentrated and the residue was purified by flash chromatography (PE/EA = 2/1) to afford **41e** (238 mg, 54% yield) as a white solid. LC-MS (ESI, Method 4) $t_R = 2.00$ min, m/z (M+H)⁺ = 217.1.

Step 5. 2,2,2-Trifluoro-1-(3-nitropyrazolo[1,5-*a*]pyridin-5-yl)ethan-1-ol (41f)

[00397] To a solution of **41e** (100 mg, 0.46 mmol) in TFA (5 mL) was added KNO₃ (56 mg, 0.56 mmol) at r.t. The reaction was stirred at 25 °C for 2 h. The resulting solution was added into H₂O (10 mL) and the pH was adjusted to 8-9 with *sat.* Na₂CO₃ solution. The mixture was

extracted with EA (20 mL*2). The combined organic phase was concentrated and the residue was purified by flash chromatography (PE/EA = 1/1) to afford **41f** (100 mg, 83% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 2.33 min, m/z (M+H)⁺ = 262.0.

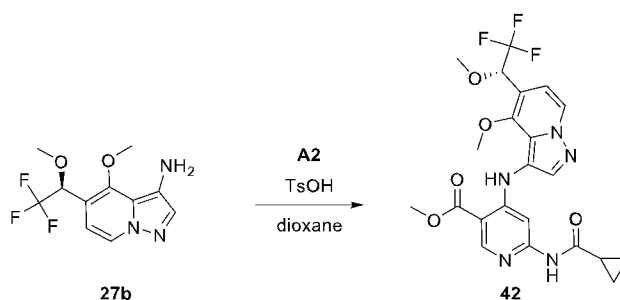
Step 6. 1-(3-Aminopyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethan-1-ol (41g**)**

[00398] To a solution of **41f** (100 mg, 0.38 mmol) in methanol (10 mL) was added Pd/C (10% on carbon, wetted with ca. 55% water) (8 mg) under H₂ atmosphere. The mixture was stirred at 25 °C for 3 h. The catalyst was filtered off and the filtrate was condensed by vacuum to give **41g** (100 mg, crude) as a brown solid, which was used in the next step without further purification. LC-MS (ESI, Method 4) t_R = 0.38 min, m/z (M+H)⁺ = 232.0.

Step 7. 6-(Cyclopropanecarboxamido)-*N*-(methyl-*d*₃)-4-((5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)nicotinamide (41**)**

[00399] To a solution of **Int. A** (15 mg, 0.058 mmol), 4-methylbenzenesulfonic acid (10 mg, 0.058 mmol) in dioxane (4 mL) was added **41g** (27 mg, 0.12 mmol) at r.t. The mixture was stirred at 100 °C for 3 h. The resulting solution was added into H₂O (20 mL) and extracted by EA (30 mL). The combined organic layer was washed by brine (20 mL*2), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by flash chromatography and then *prep*-HPLC (Method E) to afford **41** (6.4 mg, 24% yield) as a light pink solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 10.09 (s, 1H), 8.71 (d, *J* = 7.2 Hz, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 8.09 (s, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.43 (s, 1H), 7.06 (d, *J* = 6.0 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 5.36-5.27 (m, 1H), 1.94-1.85 (m, 1H), 0.73-0.62 (m, 4H). LC-MS (ESI, Method 4) t_R = 1.47 min, m/z (M+H)⁺ = 452.2.

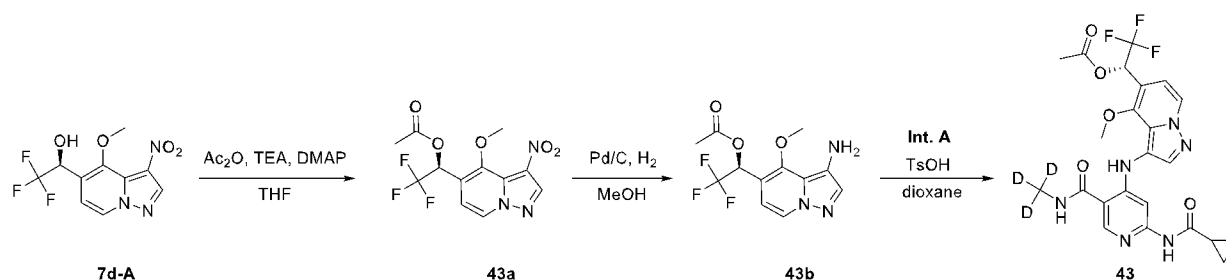
Example 42



Step 1. Methyl (*S*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-*a*]pyridin-3-yl)amino)nicotinate (42)

[00400] To a solution of **27b** (70 mg, 0.25 mmol) and **A2** (45 mg, 0.18 mmol) in dioxane (2 mL) was added TsOH (48 mg, 0.28 mmol), the mixture was stirred at 85 °C for 3 h. The mixture was condensed by vacuum and the residue was purified by *prep*-HPLC (Method E) to give **42** (30 mg, 24% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.81 (s, 1H), 9.57 (s, 1H), 8.64 (s, 1H), 8.53 (d, *J* = 7.2 Hz, 1H), 8.14 (s, 1H), 7.64 (s, 1H), 6.76 (d, *J* = 7.2 Hz, 1H), 5.25 (q, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.30 (s, 3H), 1.95-1.84 (m, 1H), 0.75-0.57 (m, 4H). LC-MS (ESI, Method 4) *t*_R = 2.82 min, *m/z* (M+H)⁺ = 494.3.

Example 43



Step 1. (*S*)-2,2,2-trifluoro-1-(4-methoxy-3-nitropyrazolo[1,5-*a*]pyridin-5-yl)ethyl acetate (43a)

[00401] To a solution of **7d-A** (150 mg, 0.52 mmol), TEA (261 mg, 2.58 mmol, 0.36 mL) and DMAP (6 mg, 0.052 mmol) in THF (5 mL) was added Ac₂O (526 mg, 5.15 mmol, 0.49 mL), the mixture was stirred at 55 °C for 2 h. The mixture was quenched with *sat.* NaHCO₃ (20 mL) and extracted with EtOAc (30 mL*2). The combined organic layer was washed with brine (20 mL*2), dried and condensed by vacuum. The residue was purified by flash chromatography (EtOAc in PE is 20%) to give **43a** (149 mg, 87% yield) as a yellow solid. LC-MS (ESI, Method 4) *t*_R = 2.95 min, *m/z* (M+H)⁺ = 334.1.

Step 2. (*S*)-1-(3-amino-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethyl acetate (43b)

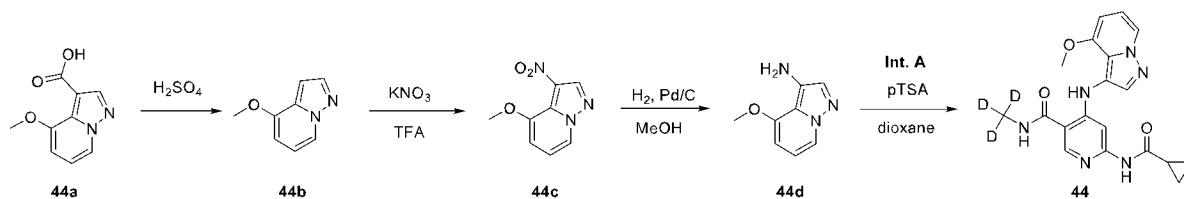
[00402] To a solution of **43a** (90 mg, 0.27 mmol) in MeOH (4 mL) was added Pd/C (9 mg, 0.081 mmol, 10% on carbon, wetted with ca. 55% water) under H₂ atmosphere. The mixture was

stirred at 25 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated to give **43b** (70 mg, 85% yield) as a brown oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) $t_R = 2.18$ min, m/z (M+H)⁺ = 304.1.

Step 3. (S)-1-(3-((2-(cyclopropanecarboxamido)-5-((methyl-*d*₃)carbamoyl)pyridin-4-yl)amino)-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)-2,2,2-trifluoroethyl acetate (43**)**

[00403] To a solution of **43b** (70 mg, 0.23 mmol) and **Int. A** (41 mg, 0.16 mmol) in dioxane (4 mL) was added TsOH (44 mg, 0.25 mmol). The mixture was stirred at 85 °C for 3 h. The mixture was condensed by vacuum and the residue was purified by *prep*-HPLC (Method E) to give **43** (45 mg, 37% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.71 (s, 1H), 10.41 (s, 1H), 8.58 (s, 1H), 8.55 (d, $J = 7.2$ Hz, 1H), 8.52 (s, 1H), 8.17 (s, 1H), 7.71 (s, 1H), 6.83 (d, $J = 7.2$ Hz, 1H), 6.59 (q, $J = 7.2$ Hz, 1H), 3.78 (s, 3H), 2.20 (s, 3H), 1.97-1.89 (m, 1H), 0.78-0.66 (m, 4H). LC-MS (ESI, Method 4) $t_R = 2.34$ min, m/z (M+H)⁺ = 524.4.

Example 44



Step 1. 4-Methoxypyrazolo[1,5-*a*]pyridine (44b**)**

[00404] Heat a well-stirred solution of **44a** (200 mg, 1.04 mmol) in 1 mL of 50% H₂SO₄ at 100 °C for 1 h. A brown solution was formed. Cool down the solution to room temperature. Neutralize the solution with aq. NaOH (1.0 M) using litmus paper as the indicator. Add 40 mL of water to the above solution. Extract the solution by EtOAc (30 mL*3). Combine the organic layer. Dry the organic layer over anhydrous Na₂SO₄. Filter the organic layer through a pad of celite. Evaporate the organic layer in vacuum to give **44b** (45 mg, 94% yield) as a colorless oil. LC-MS (ESI, Method 4) $t_R = 2.01$ min, m/z (M+H)⁺ = 149.1.

Step 2. 4-Methoxy-3-nitro-pyrazolo[1,5-*a*]pyridine (44c**)**

[00405] A mixture of **44b** (145 mg, 0.98 mmol) in TFA (2 mL) was added into KNO₃ (89 mg, 0.88 mmol) at 20 °C. The resulting mixture was stirred at 30 °C for 1 h. A yellow solution was formed. The reaction mixture was quenched with aq. NaHCO₃ (50 mL) and extracted with

EtOAc (30 mL*3). The combined organic layer was washed with brine (40 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 20-60%) to give **44c** (80 mg, 42% yield) as a yellow solid. LC-MS (ESI, Method 4) $t_R = 1.78$ min, m/z (M+H)⁺ = 194.1.

Step 3. 4-Methoxypyrazolo[1,5-*a*]pyridin-3-amine (**44d**)

[00406] A mixture of **44c** (50 mg, 0.26 mmol) and Pd/C (5 mg, 10% Pd (dry basis), wetted with 55% H₂O) in MeOH (3 mL) was degassed and purged with hydrogen for 3 times. The resulting mixture was stirred at 40 °C under H₂ atmosphere for 12 h. A black suspension was formed. The reaction mixture was filtered and concentrated. The residue was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **44d** (20 mg, 47% yield) as a red solid. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, $J = 7.2$ Hz, 1H), 7.46 (s, 1H), 6.43 (t, $J = 7.2$ Hz, 1H), 6.40 (d, $J = 7.6$ Hz, 1H), 3.92 (s, 3H), 3.56 (brs, 2H). LC-MS (ESI, Method 4) $t_R = 0.43$ min, m/z (M+H)⁺ = 164.1.

Step 4. 6-(Cyclopropanecarboxamido)-4-((4-methoxypyrazolo[1,5-*a*]pyridin-3-yl)amino)-*N*-(methyl-*d*₃)nicotinamide (**44**)

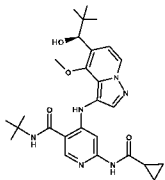
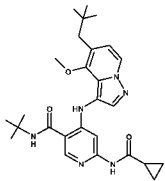
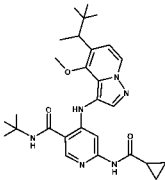
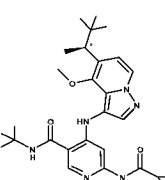
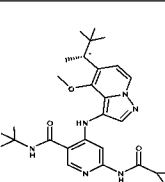
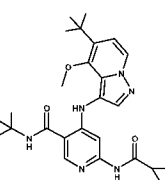
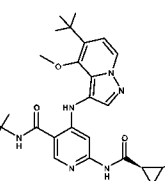
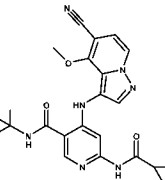
[00407] A mixture of **44d** (20 mg, 0.12 mmol), **Int. A** (31 mg, 0.12 mmol) and pTSA (42 mg, 0.24 mmol) in dioxane (2 mL) was stirred at 100 °C for 12 h. A yellow suspension was formed. The reaction mixture was diluted with aq. NaHCO₃ (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (60 mL*2) and brine (50 mL*2), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) and recrystallized in MeCN to give **44** (26.5 mg, 56% yield) as a light-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.69 (s, 1H), 10.58 (s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 8.19 (d, $J = 6.8$ Hz, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 6.78 (t, $J = 7.2$ Hz, 1H), 6.53 (d, $J = 7.6$ Hz, 1H), 3.86 (s, 3H), 2.00-1.93 (m, 1H), 0.78-0.73 (m, 4H). LC-MS (ESI, Method 4) $t_R = 4.92$ min, m/z (M+H)⁺ = 384.3.

[00408] A Summary of representative compounds are shown in **Table 1**.

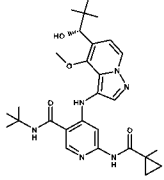
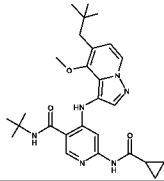
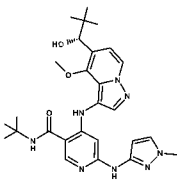
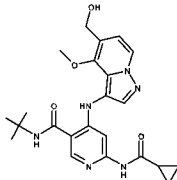
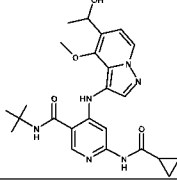
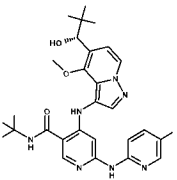
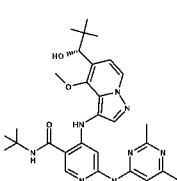
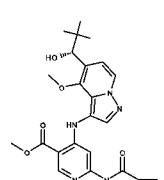
Table 1. Exemplary Compounds

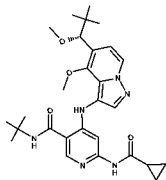
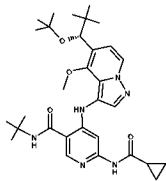
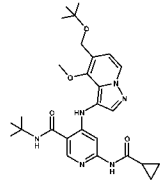
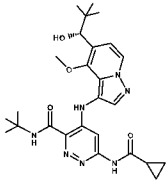
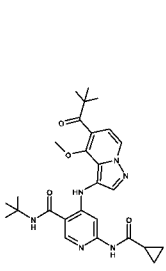
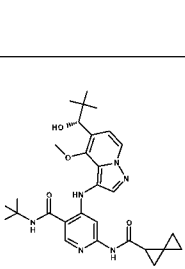
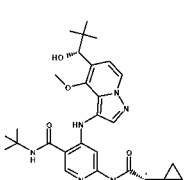
Example	Structure	Name	Mol Weight
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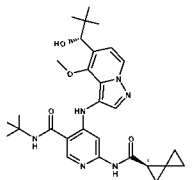
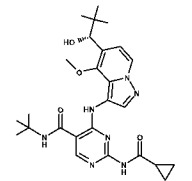
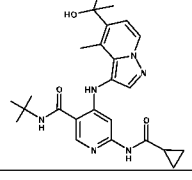
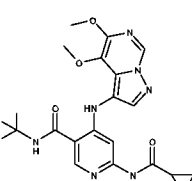
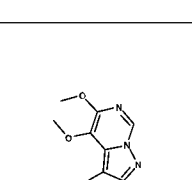
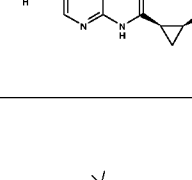
1		6-(Cyclopropanecarboxamido)-4-((4-methoxy-1-methyl-1H-indol-3-yl)amino)-N-methylpyridazine-3-carboxamide	394.43
2		6-(Cyclopropanecarboxamido)-4-((5-ethyl-4-methoxy-1-methyl-1H-indol-3-yl)amino)-N-(methyl-d3)nicotinamide	424.51
3		4-((5-Chloro-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide	417.86
4		4-((5-Chloro-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-2-(cyclopropanecarboxamido)-N-(methyl-d3)pyrimidine-5-carboxamide	418.85
5		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-methylpyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	397.44
6		Methyl 3-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-4-methoxypyrazolo[1,5-a]pyridine-5-carboxylate	441.45
7		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	481.44
7A		(S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	481.44

7B		(R)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	481.44
8		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoroethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	465.44
9		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	479.47
9A		(R*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	479.47
9B		(S*)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	479.47
10		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	451.42
11		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(trifluoromethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	469.41
12		4-((5-Cyano-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide	408.43

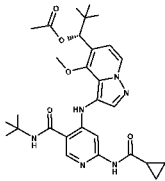
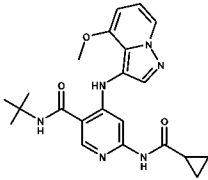
13		4-((5-Cyano-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d3)nicotinamide	426.42
14A		(S)-6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-5-yl)amino)-N-methylnicotinamide	478.42
14B		(R)-6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-5-yl)amino)-N-methylnicotinamide	478.42
15A		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	499.43
15B		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	499.43
16		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(methoxymethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	427.47
17		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(methoxymethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	445.46
18		4-((5-(Cyanomethyl)-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide	422.45

19		(S)-6-(1-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	499.43
20		6-(Cyclopropanecarboxamido)-4-((5-(2,2-difluoropropyl)-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	461.48
21		(S)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)-6-((1-methyl-1H-pyrazol-3-yl)amino)nicotinamide	493.46
22		6-(Cyclopropanecarboxamido)-4-((5-(hydroxymethyl)-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	413.44
23		6-(Cyclopropanecarboxamido)-4-((5-(1-hydroxyethyl)-4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	427.47
24		(S)-6-((5-fluoropyridin-2-yl)amino)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	508.44
25		(S)-6-((2,6-Dimethylpyrimidin-4-yl)amino)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	519.49
26		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)nicotinate	479.41

27		(S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	495.47
28		(S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-(methoxy-d3)ethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	498.49
29		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-((methoxy-d3)methyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	430.49
30		(S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide	482.43
31		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoroacetyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide and 6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1,1-dihydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	479.43
32		4-((4-Methoxy-5-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)-6-(spiro[2.2]pentane-1-carboxamido)nicotinamide	507.48
32A		4-((4-Methoxy-5-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)-6-((S*)-spiro[2.2]pentane-1-carboxamido)nicotinamide	507.48

32B		4-((4-Methoxy-5-((S)-2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)-6-((R*)-spiro[2.2]pentane-1-carboxamido)nicotinamide	507.48
33		(S)-2-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide	482.43
34		6-(Cyclopropanecarboxamido)-4-((5-(2-hydroxypropan-2-yl)-4-methylpyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	425.50
35		6-(Cyclopropanecarboxamido)-4-((4,5-dimethoxypyrazolo[1,5-c]pyrimidin-3-yl)amino)-N-(methyl-d3)nicotinamide	414.43
36		4-((4,5-Dimethoxypyrazolo[1,5-c]pyrimidin-3-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d3)nicotinamide	432.42
37		6-(Cyclopropanecarboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-3-yl)amino)-N-(methyl-d3)nicotinamide	480.46

38		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-3-yl)amino)-N-(methyl-d3)nicotinamide	498.45
39		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-c]pyrimidin-3-yl)amino)-N-(methyl-d3)nicotinamide	500.42
40		6-(Cyclopropanecarboxamido)-N-(methyl-d3)-4-(pyrazolo[1,5-a]pyridin-3-ylamino)nicotinamide	353.39
41		6-(Cyclopropanecarboxamido)-N-(methyl-d3)-4-((5-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)nicotinamide	451.42
42		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-1-methoxyethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)nicotinate	493.43

43		(S)-1-(3-((2-(cyclopropanecarboxamido)-5-((methyl-d3)carbamoyl)pyridin-4-yl)amino)-4-methoxypyrazolo[1,5-a]pyridin-5-yl)-2,2,2-trifluoroethyl acetate	523.48
44		6-(cyclopropanecarboxamido)-4-((4-methoxypyrazolo[1,5-a]pyridin-3-yl)amino)-N-(methyl-d3)nicotinamide	383.42

Binding Activity test for JH2 domain of JAK1 and TYK2

[00409] The compounds are prepared in DMSO for 200x top dose, then serial dilute it with 27-fold for 3 more points. Add 8μL/well in echo source plate, echo will add 75nL/well with 3-fold serial dilution for 11 points in assay plate. 75nL DMSO for high control and low control.

[00410] Prepare 3X working solutions (1.5nM) of JAK1-JH2 domain or TYK2-JH2 domain enzyme in assay buffer, add 5μL of enzyme working solutions per well to the assay plate including high control. For low control, add 5μL/well assay buffer. And then spin down at 1000rpm and centrifuge for 30 seconds. After enzyme system prepared, add 5μL of Tb-antibody solution into each well of assay plate. Spin down at 1000 rpm and centrifuge for 30sec. After Tb-antibody added, also add 5μL of tracer into the assay plate. Spin down at 1000rpm and centrifuge for 30sec. Incubate for 60mins at 25°C firstly and then continue to incubate the plate at 4°C overnight. Read by envision in FRET mode. The Luminescence value was recorded by a multi-label reader Envision (PerkinElmer). Inhibition Rate was calculated relative to vehicle (DMSO) treated control wells using following formula:

$$\% \text{ Inhibition} = 100 - \frac{\text{RLU}_{\text{compound}} - \text{RLU}_{\text{low control}}}{\text{RLU}_{\text{high control}} - \text{RLU}_{\text{low control}}} \times 100\%$$

wherein

RLU_compound = the relative light unit of cells treated with test compounds

RLU_low control = the relative light unit of medium with DMSO only

RLU_high control = the relative light unit of cells treated with DMSO only

[00411] The dose-response (percent inhibition) curve was plotted and IC₅₀ values (the concentration that causes 50% growth inhibition) were determined by GraphPad software. The IC₅₀ of tested compounds are shown in **Table 2**.

Table 2. IC₅₀ on JH2 domain activity (nM)

Example	TYK2 JH2 Binding IC ₅₀ (nM)	JAK1 JH2 Binding IC ₅₀ (nM)	JAK1/TYK2 selectivity
1	2.331	19.527	8.4
2	0.333	5.236	15.7
3	0.223	13.352	59.9
4	0.164	15.329	93.5
5	0.137	6.619	48.3
6	0.482	7.446	15.4
7	0.147	11.007	74.9
7A	0.097	10.436	107.6
7B	0.528	12.867	24.4
8	0.106	3.39	32.0
9	0.158	8.756	55.4
9A	0.424	38.961	91.9
9B	0.08	5.039	63.0
10	0.224	9.706	43.3
11	0.182	17.571	96.5
12	0.308	21.084	68.5
13	0.172	20.978	122.0
14A	0.102	10.344	101.4
14B	0.583	15.254	26.2
15A	0.078	12.545	160.8
15B	0.375	19.977	53.3
16	0.22	14.081	64.0
17	0.102	12.745	125.0
18	0.13	1.627	12.5
19	0.273	276.237	1011.9
20	0.058	13.643	235.2
21	0.077	10.986	142.7

22	0.185	7.505	40.6
23	0.185	13.455	72.7
24	0.066	18.599	281.8
25	0.068	11.497	169.1
26	0.183	61.869	338.1
27	0.064	8.191	128.0
28	0.073	7.483	102.5
29	0.219	16.734	76.4
30	0.088	10.948	124.4
31	0.183	149.259	815.6
32	0.171	23.455	137.2
32A	0.099	18.574	187.6
32B	0.108	11.469	106.2
33	0.082	34.303	418.3
34	161.249	>298.5	/
35	8.274	92.335	11.2
36	4.548	254.872	56.0
37	1.648	110.61	67.1
38	0.761	143.581	188.7
39	0.561	>298.5	/
40	186.126	>298.5	/
41	46.84	>298.5	/
42	0.202	79.026	391.2
43	0.175	71.263	407.2
44	2.8	60.185	21.5

[00412] Exemplary compounds of the invention showed good selectivity over JAK1. These compounds can be used to reduce or eliminate the side effects caused by JAK1 inhibition in autoimmune disease.

Biochemical assay

Testing for JAK1, JAK2 and TYK2 Kinase Activities

[00413] JAK activity was determined in the reaction buffer 50 mM HEPES, 0.01% Brij35, 10 mM MgCl₂, 2 mM DTT by a microfluidic assay. The phosphorylation of a FAM labeled peptide substrate was monitored in the Caliper EZ Reader II (Perkin Elmer). The assay condition for

each batch of enzyme (Carna Biosciences) was optimized to obtain 10% conversion rate of peptide substrate.

[00414] The test compounds were dissolved in DMSO to a stock concentration of 10 mM. Three-fold serially diluted compounds with top concentration of 5 μ M were pre-incubated with JAK1, JAK2 or TYK2 for 10 min at ambient temperature. The final DMSO concentration of assay mixture was 1%. FAM labeled peptide substrate (final concentration 3 μ M) and ATP (Km concentration or 1mM) were sequentially added to initiate the kinase reaction at 28°C for 90 min (JAK), 15 min (JAK2) and 30 min (TYK2), respectively. The reaction was stopped by adding 50 mM EDTA.

[00415] The well in the test plate without enzyme was defined as 100% inhibition. And the well without compound but with equivalent DMSO was defined as no inhibition. The percent inhibition was calculated by the following formula:

$$\% \text{ Inhibition} = \frac{\text{Conversion\%}_{\text{max}} - \text{Conversion\%}_{\text{sample}}}{\text{Conversion\%}_{\text{max}} - \text{Conversion\%}_{\text{min}}} \times 100$$

wherein

Conversion%_{max} = the conversion rate in the positive well without addition of compound

Conversion%_{sample} = the conversion rate of test compounds

Conversion%_{min} = the conversion rate in the well without addition of enzyme

[00416] The dose-response (percent inhibition) curve was plotted and IC₅₀ values were determined by GraphPad software. The IC₅₀ values of tested compounds were list in **Table 3**.

Table 3. JAK1, JAK2 and TYK2 IC₅₀ Values of Illustrative Compounds

Example	JAK1 (10 nM) (1 mM ATP), nM	JAK2 (1.5 nM) (1 mM ATP), nM	TYK2 (20 nM) (1 mM ATP), nM
7A	>20000	>20000	>20000
7B	>20000	>20000	>20000
21	>20000	>20000	>20000
25	>20000	>20000	>20000
27	>20000	>20000	>20000
30	>20000	>20000	>20000

[00417] Exemplary compounds of the invention showed excellent selectivity over JAK1, JAK2 and TYK2 kinase domain inhibition.

Anti-proliferative assay

[00418] Dimerization domain of Tel protein fused with JAK kinase domain was permanently transduced into Ba/F3 cells, whose proliferation is dependent on JAK activity in the absence of IL-3 induction. These engineered Ba/F3-FL-TYK2-P760L cells were used to monitor JAK inhibitory activities of the compounds in the cellular. Ba/F3 cells were cultured in RPMI-1640 (Corning) containing 10% fetal bovine serum. Cells were seeded at 2000/well of white flat bottom 96-well plates. The well containing medium only was used as background control. After 24h growth, cells were treated with compounds. The test compounds were dissolved in DMSO to a stock concentration of 20 mM. 3-fold serially diluted compounds for 9 concentrations with top concentration of 20 μ M was added into the each well. The final DMSO concentration was 0.1%. The cells continued to grow at 37°C in 5% CO₂ for 72 h after compound treatment. The viability was measured by cellular ATP determination using the Cell-Titer Glo luciferase reagent (Promega). The Luminescence value was recorded by a multi-label reader Envision (PerkinElmer). Inhibition Rate was calculated relative to vehicle (DMSO) treated control wells using following formula:

$$\% \text{ Inhibition} = 100 - \frac{\text{RLU}_{\text{compound}} - \text{RLU}_{\text{blank}}}{\text{RLU}_{\text{control}} - \text{RLU}_{\text{blank}}} \times 100\%$$

wherein

RLU_{compound} = the relative light unit of cells treated with test compounds

RLU_{blank} = the relative light unit of medium with DMSO only

RLU_{control} = the relative light unit of cells treated with DMSO only

[00419] The dose-response (percent inhibition) curve was plotted and IC₅₀ values (the concentration that causes 50% growth inhibition) were determined by GraphPad software. The IC₅₀ of tested compounds are shown in **Table 4**.

Table 4. Ba/F3-FL-TYK2-P760L Cells IC₅₀ Values of Exemplary Compounds

Example	Baf3-FL-T2P760L (nM)	Example	Baf3-FL-T2P760L (nM)
1	1173	21	15.69
2	17.04	22	127.4
3	43.65	23	165.7

4	38.92	24	3.87
5	31.99	25	5.01
6	146.4	26	35.25
7	9.32	27	8.54
7A	5.4	28	10.67
7B	223.25	29	80.945
8	31.26	30	7.96
9	51.65	31	60.26
9A	2142	32	42.31
9B	54.19	32A	33.03
10	119.5	32B	27.34
11	54.49	33	16.02
12	193.6	34	>5000.0
13	130.9	35	2344
14A	7.41	36	1768
14B	207.2	37	767.7
15A	10.58	38	1345
15B	870.4	39	350.5
16	87.03	40	>5000.0
17	84.28	41	>5000.0
18	90.28	42	104.4
19	137.3	43	20.6
20	23.13	44	356.2

IFN- γ Release in NK92 Cells Stimulated by IL-12

[00420] *Purpose:* To evaluate the inhibition activity of TYK2 inhibitors in NK92 cells on TYK2 pathway through ELISA method.

[00421] *Materials:*

Items	Vendor	Cat. No.
PBS	BI	02-024-01ACS
α -MEM	Gibco	12561056
Inactivated Horse Serum	Gibco	26050088
FBS	Gibco	10091148
β - Mercaptoethanol	procell	PB180633
Penicillin-Streptomycin	Gibco	15140-122
Folic Acid	MCE	HY-16637A
i-Inositol	MCE	HY-B1411
Recombinant human IL-2	PEPROTECH	200-02-10UG
Recombinant human IL-12 P70	PEPROTECH	200-12-50UG
ELISA MAX TM Deluxe Set Human IFN- γ	BD	555142

Nunc Edge 2 96-well plate	Thermo	167425
TMB	Solarbio	PR1200
ELISA Plate	Corning	9018
Stop Solution	Elabscience	E-ELIR-006

[00422] *Procedure:* 1) Seeding NK92 cells into 96-well plate, cell density is 1.5E5 cells/well, 100uL/well; 2) Add prepared test articles into indicated wells, 50uL/well, and continue incubate for 1h, at 37°C; 3) After compound treatment, add 50uL/well IL-12 into indicated wells, final concentration of IL-12 is 2.5ng/mL; 4) Incubate cytokine stimulated cells at 37°C for another 15hrs in CO₂ incubator; 5) After cytokine stimulation, transfer culture supernatant into a new plate and centrifuge for 5min at 350x g, and detect IFN- γ concentration in the supernatant with ELISA kit; 6) Data analysis with GrapdPad Prism6.0 software.

Table 5. IC₅₀ Values of Exemplary Compounds on TYK2 pathway

Example	IC ₅₀ on TYK2 pathway (nM)
7A	9.10
15A	15.70
21	14.49
25	7.18
26	17.6
27	6.02
30	6.72

[00423] Exemplary compounds of the invention showed good TYK2 pathway inhibition activity in cells.

Phosphorylation Inhibition of STAT in Human Whole Blood Testing:

[00424] The inhibitory potential of test articles in human whole blood assay was evaluated by the method of flow cytometry.

[00425] IFN- α will activate JAK1 and TYK2 kinase in T cells by binding to IFN receptors, and then lead to phosphorylation of STAT1 and STAT2. The phosphorylated STAT1 enter nuclear and promote transcription and expression of IFN- γ . To evaluate the efficacy of TYK2i in T cells, freshly collected human whole blood will be stimulated with certain unit of human IFN- α (Universal Type I IFN(1MU), R&D, 11200-2) for 20 mins in incubator. After

stimulation, fix cells with Phosflow™ Fix Buffer I (BD, 557870), and then collect fixed cells by centrifugation (500 g, 8min). Wash cells once with pre-cooled PBS, and then permeabilize cells with cold Perm Buffer III buffer (BD, 558050) for 45 mins on ice. Collect cells by centrifugation (600 g, 8min) and washed twice with cold PBS. Stain cells with anti-human CD3(FITC Mouse Anti-Human CD3, BD, 555332) and anti-pSTAT1_Y701(Alexa Fluor 647 Mouse Anti-Stat1 (pY701), BD, 612597) antibodies. Detect pSTAT1 by flow cytometry (CytoFlex S) and analyze data with FlowJo and GraphPad Prism 8 software. IC50 values of test articles were determined using 4- parameter logistic equation.

[00426] Exemplary results are summarized in **Table 6**.

Table 6

Example	pSTAT1 inhibition in hWB (IC50,nM)	Example	pSTAT1 inhibition in hWB (IC50,nM)
2	140.66	18	84.33
3	176.6	21	25.87
4	312.3	22	80.81
5	139.34	24	34.58
7	67.43	25	30.83
7A	45.28	27	51.22
7B	1005	30	52.21
8	75.46	31	863.3
9B	289.7	32A	99.43
14A	35.91	18	84.33
15A	34.83	43	173.8

ADME

Microsomal Metabolic Stability assay

[00427] Microsomes were pre-incubated with test compound or control compounds for 5 min at 37°C in 100 mM potassium phosphate buffer, pH 7.4, 1.0 mM EDTA. The reaction was initiated by addition of 15 µL of the NADPH regenerating system to 30 µL of each incubation mixture per time point. The final incubation condition was composed of 0.5 mg/mL microsomal protein, 1 µM test article/positive control, 2 mM NADPH. The 0-minute samples were prepared by addition of a 30 µL aliquot of each incubation mixture to 135 µL quench reagent to precipitate proteins. And then a 15 µL aliquot of the NADPH regenerating system was added. At

5, 15, 30 and 45 minutes, the reaction will be stopped by the addition of cold acetonitrile solution containing internal standard. The samples taken at all time points were centrifuged at 5000×g for 15 minutes. 50 µL of supernatant are taken into 96-well assay plates pre-added with 50 µL ultrapure water, and then analyzed by LC/MS/MS.

[00428] Concentrations of test articles, control compounds in the samples were determined by using LC/MS/MS method. Plotting of the chromatograms and peak area integrations are carried out by Analyst (AB Sciex).

[00429] In the determination of the *in vitro* elimination constant (k_e) of the control compounds, the analyte/internal standard peak area ratios will be converted to percentage remaining (%Remaining) with the following equation:

$$\%Remaining = \frac{\text{Peak area ratio of analyte to IS at each time point}}{\text{Peak area ratio of analyte to IS at } t = 0} \times 100\%$$

[00430] The CL_{int} of microsomes was calculated using the formula: $CL_{int(mic)} = 0.693/T_{1/2} / \text{mg microsome protein per mL}$. The slope was measured by the natural logarithm of the percentage of the residual compound and time, $T_{1/2}$ was calculated according to the following formula.

$$T_{1/2} = \frac{0.693}{-slope}$$

[00431] Exemplary results are summarized in **Table 7**.

Table 7

Example	Human LM T1/2 (min)	Human LM Clint (uL/min/mg)
7A	88.7	15.63
7B	128.3	10.80
13	62.99	22.00
14A	74.25	18.67
15A	116.42	11.91
17	112.21	12.35
21	60.72	22.83
22	308.09	4.5
23	7938.23	0.17
24	56.24	24.64
29	49.64	27.92
30	81.46	17.01
35	242.29	5.72
37	113	12.27

38	188.78	7.34
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Kinetic solubility

[00432] Aliquots of 8 μ L of reference and test compound stock solutions (10 mM/5 mM) are added into 792 μ L of 100 mM pH 7.4 phosphate buffer. The final DMSO concentration is 1%. Sample tubes are shaken for 2 hours at 1000 rpm at room temperature. Samples are centrifuged at 12000 rpm for 10 min to precipitate un-dissolved particles. And transfer the supernatants to a new tube or plate. Add 5 μ L of samples (no diluted, 10 times diluted and 100 times diluted) and standard curve samples to 95 μ L of ACN containing IS for LC-MS/MS analysis.

Exemplary results are summarized in **Table 8**

Table 8

Example	Kinetics Solubility_PBS7.4(μ M)	Example	Kinetics Solubility_PBS7.4(μ M)
2	15.30	19	22.70
3	15.10	20	15.00
5	57.40	21	57.20
7	42.90	24	10.37
7A	52.14	25	43.00
7B	55.80	27	14.25
8	18.55	29	67.20
9	60.02	30	41.95
9A	35.80	31	39.85
9B	45.35	32	62.20
12	15.14	32A	25.50
13	11.18	33	59.35
14A	45.46	38	37.20
15A	23.91	43	33.30

[00433] Exemplary compounds of the invention showed ideal solubility for further development.

Brian Pharmacokinetic study in rats

[00434] Pharmacokinetic profiles of test articles were evaluated in fasted Sprague-Dawley rats. Formulation of 5%DMSO+65%PEG400+30%Water was designed to ensure test articles fully dissolved and wouldn't precipitate in 1:10 SGF or FaSSIF dilution. Typically, SD rats were

dosed with 3 mg/kg by intravenous injection. The animal was restrained manually at the designated time points, approximately 150 μ L of blood sample was collected via jugular vein for serial bleeding into K2EDTA tubes. Sampling at 0.083, 0.5 and 1 hr, 3 time points. The blood samples were maintained in wet ice first and centrifuged to obtain plasma (2000g, 4°C, 5 min) within 30 minutes post sampling. Anesthetizing the rat with the Isoflurane vaporizer to 2%~3% and place its back on the operation table. Spread the animal limbs and pin the limbs on the operation table. Make a cut along the sternum about 4cm long, low enough to expose the sternum's end. Expose the heart and use a 25-gauge needle connected with a 20 mL syringe filled with 20 mL of cold saline to pierce the left ventricle. Maintain the placement of the needle, and slowly push the syringe plunger to wash the brain with saline. The perfusion will be finished within about 2 min and then take the brain out of the body carefully without damaging the tissue. Dry the tissue on filtrate paper, which should be placed on ice, and then weigh the brain tissue and store at -70 °C and analyzed by LC/MS/MS for quantification. PK parameter values, including, but not necessarily limited to, the maximum plasma concentrations (C_{max}), and the area under the plasma concentration vs. time curve (AUC) from time zero to 24-hour (AUC_{0-24h}) were determined using WinNonlin program.

Table 9. Systemic Pharmacokinetic Parameters in Sprague-Dawley Rats by Intravenous Administration

Example	Final State of the Formulation	Dose (mg/kg)	AUC (h*ng/ml)	T _{1/2} (h)	V _d (L/Kg)
42	solution	3	739	0.34	1.76

Table 10. Brain Pharmacokinetic Parameters in Sprague-Dawley Rats by Intravenous Administration

Example	Final State of the Formulation	Dose (mg/kg)	C _{max} (ng/g)	T _{1/2} (h)	AUC (h*ng/g)	Brain AUC/Systemic AUC
42	solution	3	3910	0.25h	1389	1.88

[00435] Example 42 showed good brain exposure in Rats.

[00436] Applicant's disclosure is described herein in preferred embodiments with reference to the Figures, in which like numbers represent the same or similar elements. Reference throughout this specification to "one embodiment," "an embodiment," or similar language means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment," "in an embodiment," and similar language throughout this specification may, but do not necessarily, all refer to the same embodiment.

[00437] The described features, structures, or characteristics of Applicant's disclosure may be combined in any suitable manner in one or more embodiments. In the description, herein, numerous specific details are recited to provide a thorough understanding of embodiments of the invention. One skilled in the relevant art will recognize, however, that Applicant's composition and/or method may be practiced without one or more of the specific details, or with other methods, components, materials, and so forth. In other instances, well-known structures, materials, or operations are not shown or described in detail to avoid obscuring aspects of the disclosure.

[00438] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Methods recited herein may be carried out in any order that is logically possible, in addition to a particular order disclosed.

Incorporation by Reference

[00439] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, have been made in this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material explicitly set forth herein is only incorporated to the extent that no conflict arises between that incorporated material and the present disclosure material. In the event of a conflict, the conflict is to be resolved in favor of the present disclosure as the preferred disclosure.

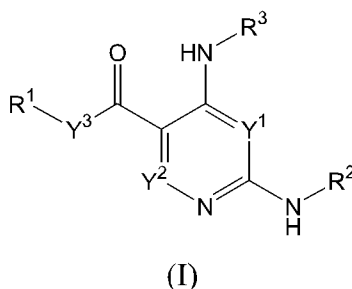
Equivalents

[00440] The representative examples are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples and the references to the scientific and patent literature included herein. The examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

What is claimed is:

CLAIMS

1. A compound having the structural formula (I):



or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

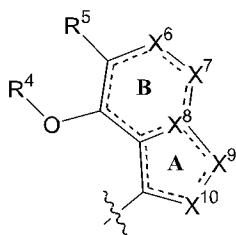
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

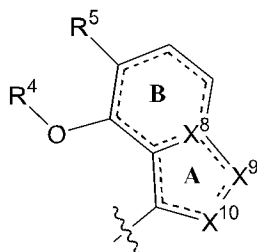
R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

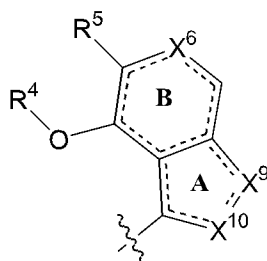
each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 .

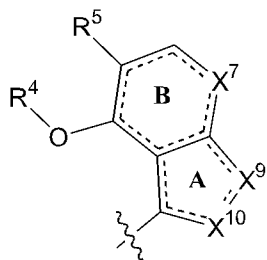
2. The compound of claim 1, wherein each of Ring A and Ring B is independently a heteroaryl group.
3. The compound of claim 1 or 2, wherein X^6 is CH and X^7 is CH, with R^3 having the structure:



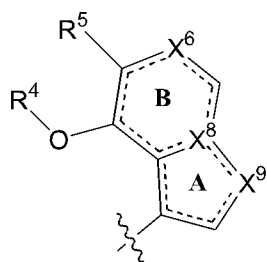
4. The compound of claim 1 or 2, wherein X^7 is CH and X^8 is C, with R^3 having the structure:



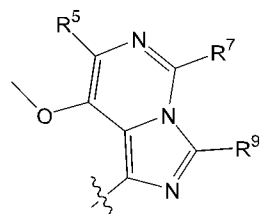
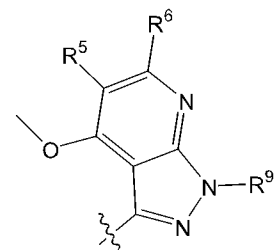
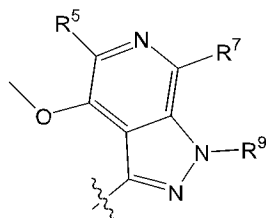
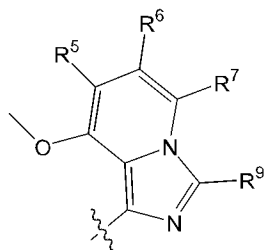
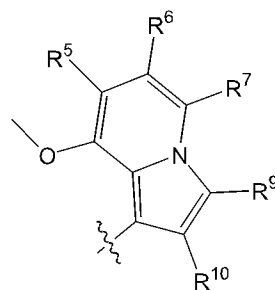
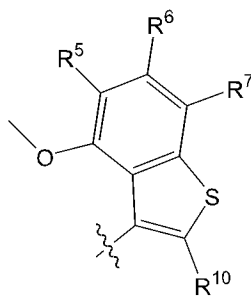
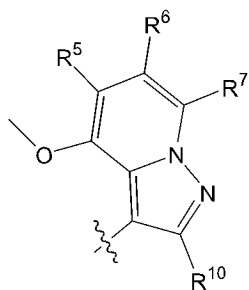
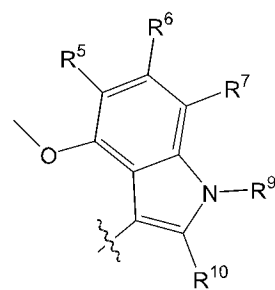
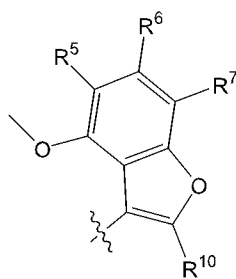
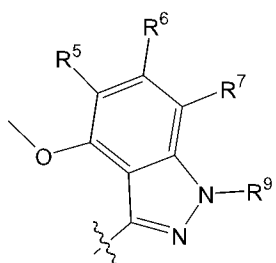
5. The compound of claim 1 or 2, wherein X^6 is CH and X^8 is C, with R^3 having the structure:



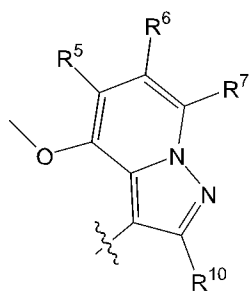
6. The compound of claim 1 or 2, wherein X^7 is CH and X^{10} is CH, with R^3 having the structure:



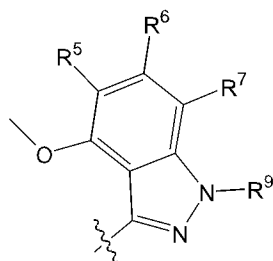
7. The compound of any one of claims 1-6, wherein R^4 is CH_3 .
8. The compound of any one of claims 1-7, wherein R^3 is selected from:



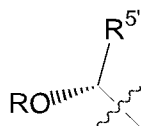
9. The compound of claim 8, wherein R^3 is:



10. The compound of any one of claims 1-9, wherein R^{10} if present is H.
11. The compound of claim 8, wherein R^3 is:



12. The compound of any one of claims 1-11, wherein R^9 if present is C_{1-3} alkyl.
13. The compound of any one of claims 1-12, wherein R^5 is a C_{1-4} alkyl, substituted with an OH.
14. The compound of claim 13, wherein R^5 is:

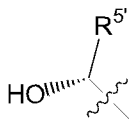


wherein

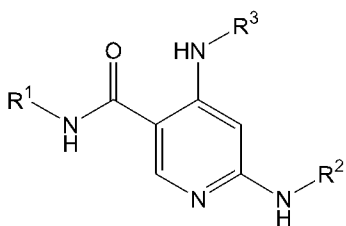
$R^{5'}$ is a C_{1-3} alkyl, substituted with 0-5 F's; and

R is H, C_{1-3} alkyl or acyl.

15. The compound of claim 14, wherein R is H and R^5 is:

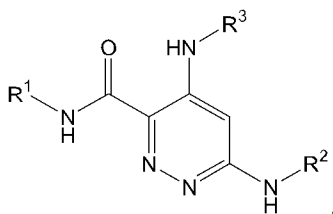


16. The compound of claim 14, wherein R is CH_3 .
17. The compound of claim 14, wherein R is $C(=O)CH_3$.
18. The compound of any one of claims 1-17, wherein Y^3 is NH.
19. The compound of claim 18, wherein Y^1 is CH and Y^2 is CH:

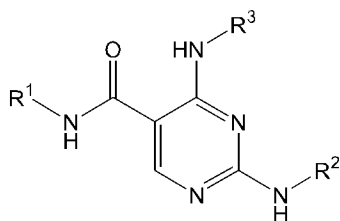


(Ia)

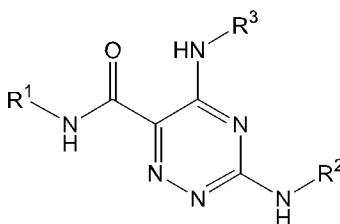
20. The compound of claim 18, wherein Y^1 is CH and Y^2 is N:

(I^b)

21. The compound of claim 18, wherein Y¹ is N and Y² is CH:

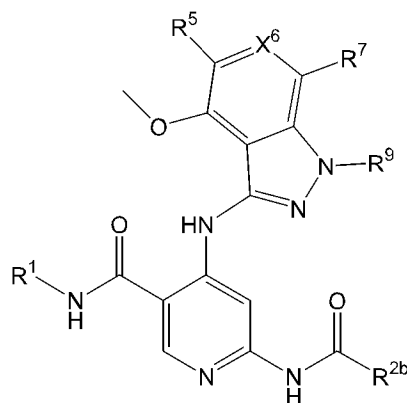
(I^c)

22. The compound of claim 18, wherein Y¹ is N and Y² is N:

(I^d)

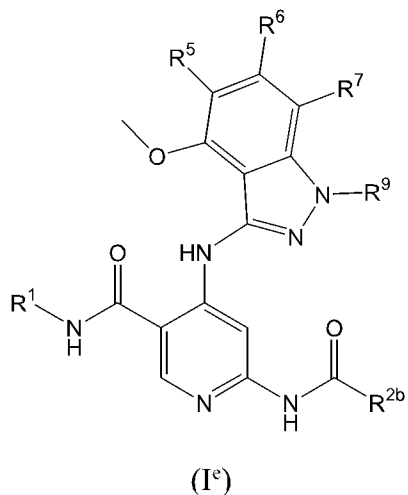
23. The compound of any one of claims 1-22, wherein R⁶ and R⁷, if present, is H.
24. The compound of any one of claims 1-23, wherein R² is R^{2'}.
25. The compound of any one of claims 1-23, wherein R² is (C=O)R^{2b}.
26. The compound of claim 25, wherein R^{2b} is selected from C₁-C₆ alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{2c}.
27. The compound of claim 26, wherein R^{2b} is cyclopropyl.
28. The compound of any one of claims 1-23, wherein R² is (C=O)NHR^{2b}.
29. The compound of any one of claims 1-23, wherein R² is pyridinyl substituted with 0-2 R^{2c}.
30. The compound of any one of claims 1-23, wherein R² is phenyl substituted with 0-2 R^{2b}.
31. The compound of any one of claims 1-23, wherein R² is pyrazolyl substituted with 0-2 R^{2c}.

32. The compound of any one of claims 1-23, wherein R² is pyrimidyl substituted with 0-2 R^{2c}.
33. The compound of any one of claims 1-32, wherein R¹ is CH₃.
34. The compound of any one of claims 1-32, wherein R¹ is CD₃.
35. The compound of claim 1, having the structural formula:

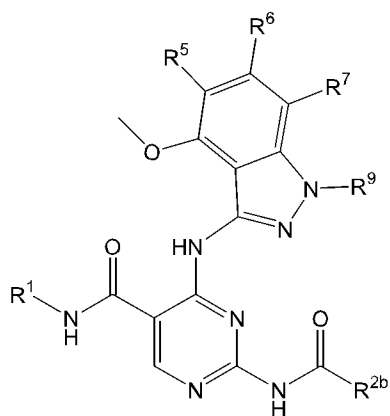


wherein X⁶ is N or CH.

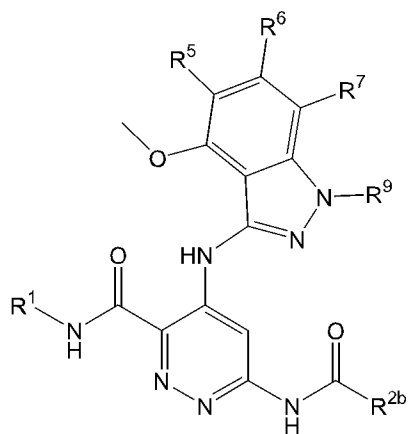
36. The compound of claim 1, having the structural formula:



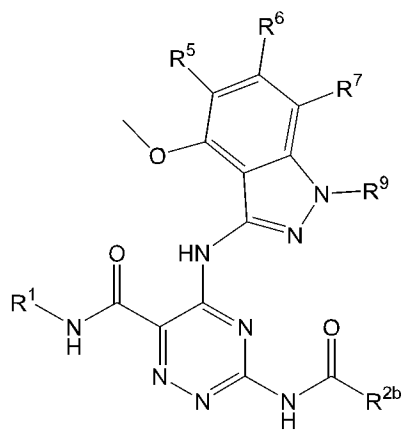
37. The compound of claim 1, having the structural formula:

(I^f)

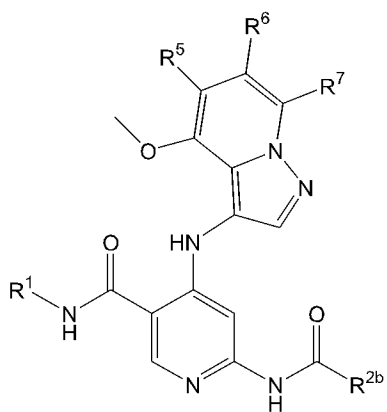
38. The compound of claim 1, having the structural formula:

(I^g)

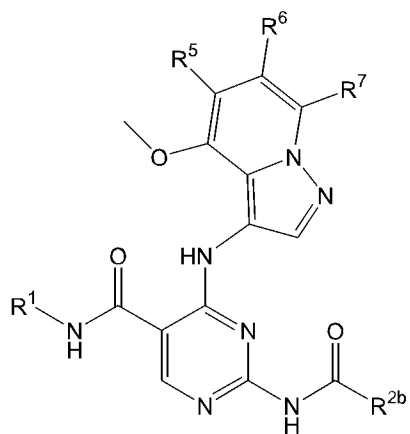
39. The compound of claim 1, having the structural formula:

(I^h)

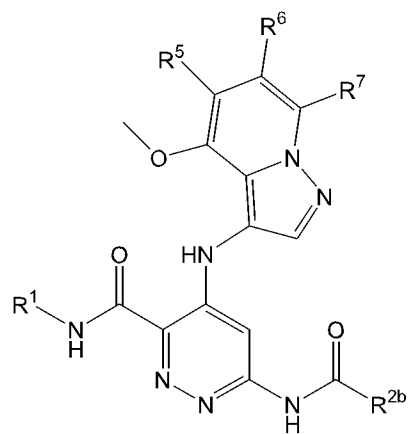
40. The compound of claim 1, having the structural formula:

(Iⁱ)

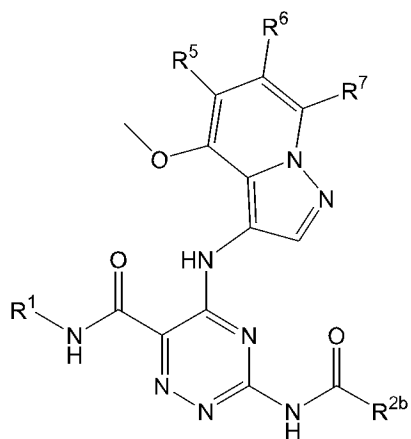
41. The compound of claim 1, having the structural formula:

(I^j)

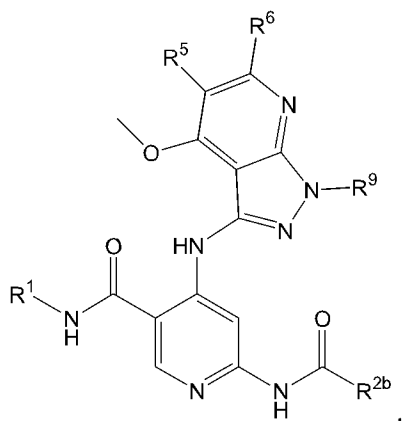
42. The compound of claim 1, having the structural formula:

(I^k)

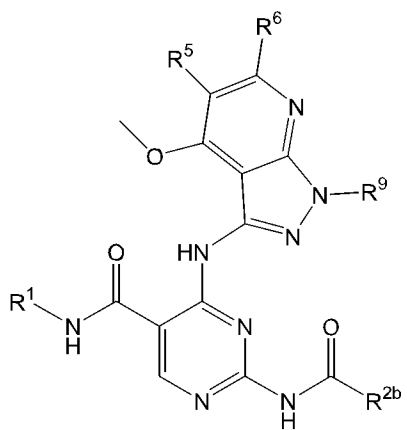
43. The compound of claim 1, having the structural formula:

(I^l)

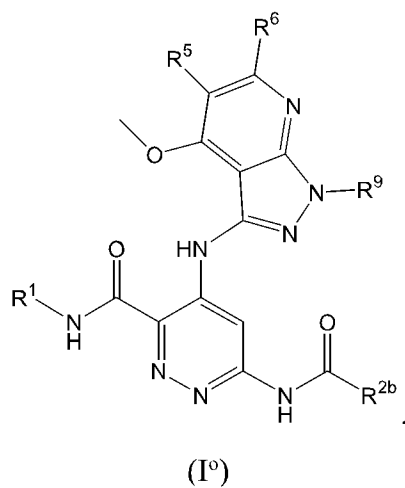
44. The compound of claim 1, having the structural formula:

(I^m)

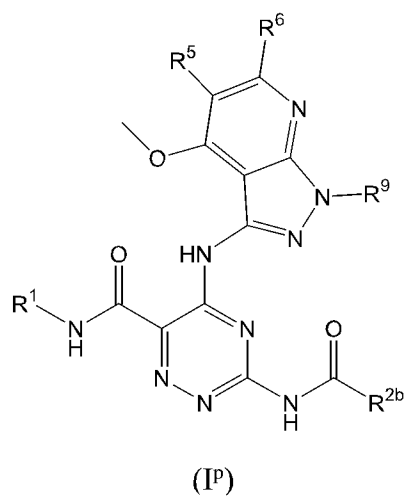
45. The compound of claim 1, having the structural formula:

(Iⁿ)

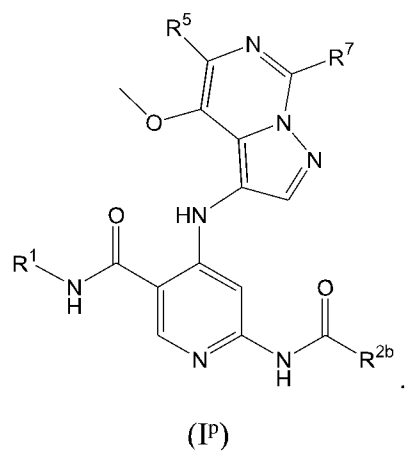
46. The compound of claim 1, having the structural formula:



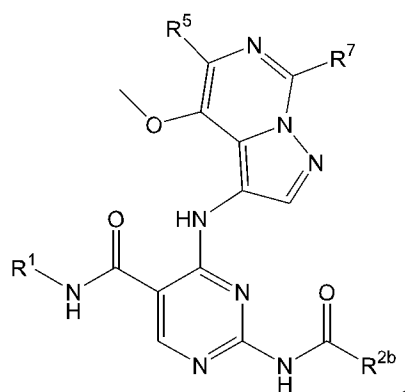
47. The compound of claim 1, having the structural formula:



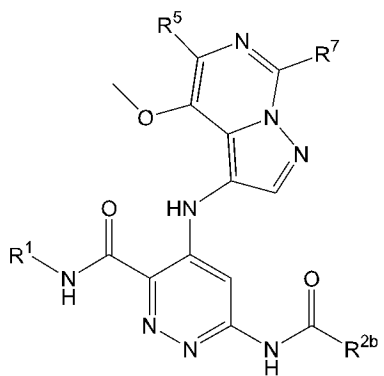
48. The compound of claim 1, having the structural formula:



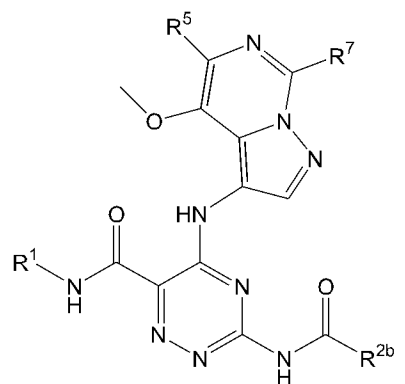
49. The compound of claim 1, having the structural formula:

(I^q)

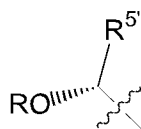
50. The compound of claim 1, having the structural formula:

(I^s)

51. The compound of claim 1, having the structural formula:

(I^t)

52. The compound of any one of claims 35-51, wherein R⁶ and R⁷, if present, is H.
53. The compound of any one of claims 35-52, wherein R^{2b} is C₁-C₆ alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{2c}.
54. The compound of any one of claims 35-53, wherein R⁵ is:

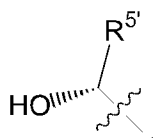


wherein

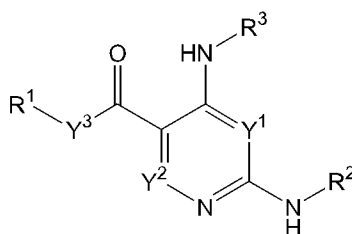
R^5 is a C_{1-3} alkyl, substituted with 0-5 F's; and

R is H, C_{1-3} alkyl or acyl.

55. The compound of claim 54, wherein R is H and R^5 is:



56. The compound of claim 54, wherein R is CH_3 .
57. The compound of claim 54, wherein R is $C(=O)CH_3$.
58. The compound of any one of claims 35-57, wherein R^1 is CH_3 .
59. The compound of any one of claims 35-57, wherein R^1 is CD_3 .
60. The compound of claim 59, wherein R^{2b} is cyclopropyl and R^5 is a C_{2-3} alkyl, substituted with 2-5 F's.
61. A compound selected from **Table 1** or a pharmaceutically acceptable form or an isotope derivative thereof. [WILL NEED TO INCLUDE A TABLE OF COMPOUNDS IN THE DESCRIPTION SECTION, WHICH WE CAN REFERENCE HERE]
62. A pharmaceutical composition comprising a compound according to any of claims 1-61, effective to treat or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.
63. A pharmaceutical composition comprising an amount of a compound having the structural formula of (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2 , CF_2 or O-NH;

R^1 is a H, F, C_1 - C_3 alkyl and CD_3 , provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

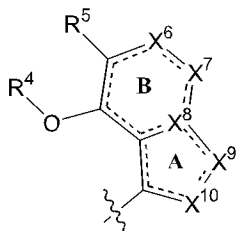
$R^{2'}$, wherein $R^{2'}$ is a C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, or C_3 - C_6 heterocycloalkyl, each substituted with 0-2 R^{2a} , wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR' , alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, C_5 - C_7 spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR' , OCF_3 , CF_3 , C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

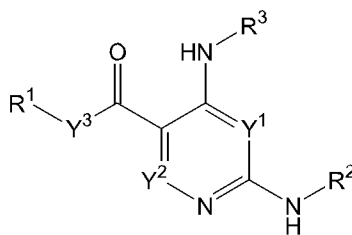
each of R^6 , R^7 , R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3 , CH_2CF_3 , CF_3 , OR, NRR' , C_1-C_3 alkyl and C_3-C_5 cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a} ; and

each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R' , together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2 , effective to treat, or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

64. The pharmaceutical composition of claim 62 or 63, being suitable for oral administration.
65. The pharmaceutical composition of claim 62 or 63, being suitable for topical administration.
66. The pharmaceutical composition of claim 62 or 63, being suitable for GI-restricted administration.
67. The pharmaceutical composition of claim 62 or 63, being useful to treat or reduce one or more of inflammatory diseases, immune-mediated diseases and cancers, or a related disease or disorder.
68. The pharmaceutical composition of claim 67, wherein the disease or disorder is an inflammatory disease.
69. The pharmaceutical composition of claim 67, wherein the disease or disorder is an immune-mediated disease.
70. The pharmaceutical composition of claim 67, wherein the disease or disorder is cancer.
71. The pharmaceutical composition of claim 67, wherein the disease or disorder is selected from: inflammatory bowel disease, psoriasis, vitiligo, atopic dermatitis, systemic lupus erythematosus, asthma, diabetic nephropathy, chronic myelogenous leukemia (CML),

essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), breast cancer and ovarian cancer.

72. A unit dosage form comprising a pharmaceutical composition according to any of claims 62-71.
73. The unit dosage form of claim 72, being a tablet.
74. The unit dosage form of claim 72, being a capsule.
75. The unit dosage form of claim 72, being a topical formulation.
76. A method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-61, wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.
77. A method for treating, reducing or preventing a disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound having the structural formula of (I):



(I)

or a pharmaceutically acceptable form or an isotope derivative thereof,
wherein

Y¹ is CH, CF or N;

Y² is CH or N;

Y³ is NR, O, CH₂, CF₂ or O-NH;

R¹ is a H, F, C₁-C₃ alkyl and CD₃, provided that R¹ is not F when Y³ is N, O or O-NH;

R² is

R^{2'}, wherein R^{2'} is a C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₅-C₇ spirocycloalkyl, or C₃-C₆ heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a}

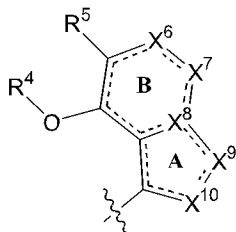
is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic;

an aryl or heteroaryl group, each substituted with 0-2 R^{2a} ;

$(C=O)R^{2b}$; or

$(C=O)NHR^{2b}$;

R^3 is



wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

X^9 is CR^9 , O, S, N or NR^9 ;

X^{10} is CR^9 , O, S, N or NR^{10} ; and

wherein each of Ring A and Ring B is independently an aryl or heteroaryl group;

R^{2b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{2c} ;

R^{2c} at each occurrence is independently halo, CN, OR, NRR', OCF_3 , CF_3 , C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' is substituted with 0-3 R^{2a} ; and

R^4 is a C_{1-3} alkyl, substituted with 0-5 R^{4a} , wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3 , $C(=O)OCH_3$, C_{1-6} alkyl, C_3-C_6 cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a} , wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, OCH_3 , OCD_3 , OCF_3 and $OC(=O)CH_3$;

each of R⁶, R⁷, R⁹ and R¹⁰ is independently selected from H, F, Cl, CN, CD₃, CH₂CF₃, CF₃, OR, NRR', C₁-C₃ alkyl and C₃-C₅ cycloalkyl, wherein said alkyl, cycloalkyl, R and R' is substituted with 0-2 R^{2a}; and

each of R and R' is independently H or a C₁-C₆ alkyl or acyl, or R and R', together with the nitrogen atom to which they are bound, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO₂, wherein the disease or disorder is selected from inflammatory diseases, immune-mediated diseases, cancer, or a related disease or disorder thereof, in a mammal, including a human.

78. The method of claim 76 or 77, wherein the disease or disorder is an inflammatory disease.
79. The method of claim 76 or 77, wherein the disease or disorder is an immune-mediated disease.
80. The method of claim 76 or 77, wherein the disease or disorder is cancer.
81. The method of claim 76 or 77, wherein the disease or disorder is selected from: inflammatory bowel disease, psoriasis, vitiligo, atopic dermatitis, systemic lupus erythematosus, asthma, diabetic nephropathy, chronic myelogenous leukemia (CML), essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), breast cancer and ovarian cancer.
82. The method of any of claims 76-81, wherein administration is via oral administration.
83. The method of any of claims 76-81, wherein administration is via topical administration.
84. The method of any of claims 76-81, wherein administration is via GI-restricted administration.
85. Use of a compound of any of claims 1-61, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
86. The use of claim 85, wherein the disease or disorder is one or more of inflammatory diseases, immune-mediated diseases and cancer.
87. The use of claim 86, wherein the disease or disorder is an inflammatory disease.
88. The use of claim 86, wherein the disease or disorder is an immune-mediated disease.
89. The use of claim 86, wherein the disease or disorder is cancer.
90. The use of any one of claims 85-89, wherein the medicament is for oral administration.

91. The use of any one of claims 85-89, wherein the medicament is for topical administration.
92. The use of any one of claims 85-89, wherein the medicament is for GI restriction administration.
93. A method for preparing a compound of any one of claims 1-61.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2023/100518

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/04(2006.01)i; C07D401/12(2006.01)i; C07D403/12(2006.01)i; C07D487/04(2006.01)i; A61K31/4439(2006.01)i; A61K31/495(2006.01)i; A61P29/00(2006.01)i; A61P35/00(2006.01)i; A61P37/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D471/-,C07D401/-,C07D403/-,A61K31/-, A61P29/-, A61P35/-, A61P37/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNTXT, DWPI, VEN, CNKI, REG, CAPLUS, substructure search according to formula (I) shown in claim 1, TYK?, cancer?, tumor?, inflammatory, immune

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 115466257 A (ACCRO BIOSCI HK LTD) 13 December 2022 (2022-12-13) see claims 1, 2, 5-12, the description examples A2, A4 and A39, tables 2 and 3	1-75, 85-92
X	CN 111484480 A (SHANGHAI HANSEN BIOLOGICAL PHARM TECHNOL et al.) 04 August 2020 (2020-08-04) see claims 1,3,12 and 15-17, compounds 44 and 45	1-75, 85-92
A	CN 115003667 A (BEIGENE CO LTD) 02 September 2022 (2022-09-02) see the whole document	1-75, 85-92



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“D” document cited by the applicant in the international application

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

05 March 2024

Date of mailing of the international search report

12 March 2024

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2023/100518

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **76-84**
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 76-84 relate to a method of treatment of the human or animal body by therapy. (see Rule 39.1.(iv))
2. ☒ Claims Nos.: **93**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 93 relates to a method for preparing a compound of any one of claims 1-61 without any technical features of preparation. Thus, no meaningful international search according to claim 93 can be carried out. (see Article 17(2)(a)(ii))
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2023/100518

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	115466257	A	13 December 2022	None			
CN	111484480	A	04 August 2020	None			
CN	115003667	A	02 September 2022	WO	2021170046	A1	02 September 2021
				US	2023159520	A1	25 May 2023