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

(57) Abstract: Provided herein are 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

Priority Claims and Related Patent Applications

[0001] This application claims the benefit of priority to PCT International application No. PCT/CN2023/100508, filed June 15, 2023, the entire content of which is incorporated herein by reference for all purposes.

Technical Fields of the Invention

[0002] 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

[0003] 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.)

[0004] 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(l):273-287.)

[0005] TYK2 is a key component of the JAK-STAT signaling pathway. TYK2 regulates INFα, 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-a, IFN-b, IFN-k, IFN-d, IFN-e, IFN-t, IFN-w, and IFN-z, and interleukins (*e.g.*, IL-4, IL-6, IL-10, IL-11, IL-12, IL-13, L-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.

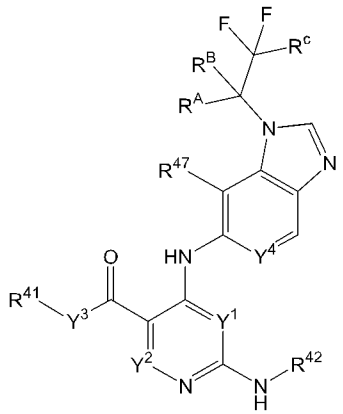
[0006] The selectivity against other JAK family subtypes is regarded as crucial in order to increase the intended pharmacological effects and to reduce side effects. Identifying kinase inhibitors with a high degree of TYK2 selectivity has posed a significant challenge partly due to the high sequence 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.)

[0007] An urgent need exists and challenges remain across broad therapeutic areas for high selective TYK2 inhibitors against other JAK family members with improved potency and minimal side effects.

Summary of the Invention

[0008] The invention provides novel, high selective and potent compounds that are orally available. These therapeutic agents are safe, effective and high selective 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.

[0009] 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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

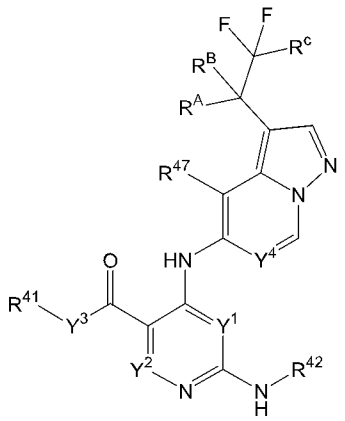
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[0010] In another aspect, the invention generally relates to a compound having the structural formula (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

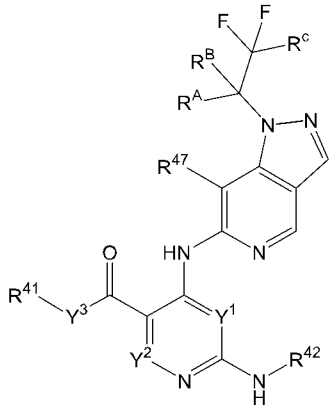
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[0011] In yet another aspect, the invention generally relates to a compound having the structural formula (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

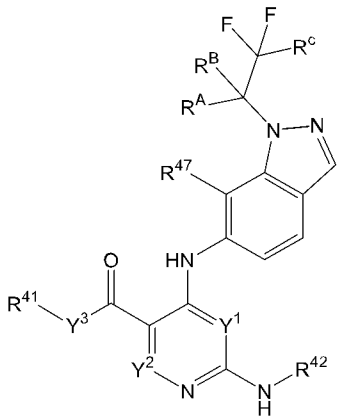
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[0012] In yet another aspect, the invention generally relates to a compound having the structural formula (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

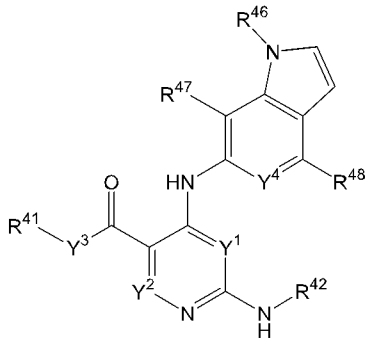
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[0013] In yet another aspect, the invention generally relates to a compound having the structural formula (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

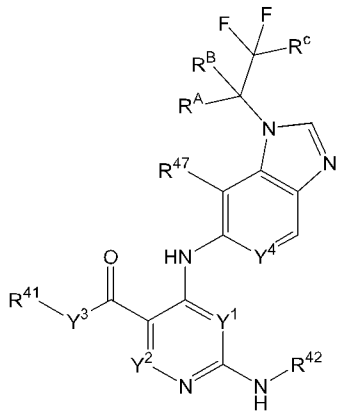
R^{48} is H, halo or a C_1-C_3 alkyl.

[0014] 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.

[0015] 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.

[0016] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[0017] 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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

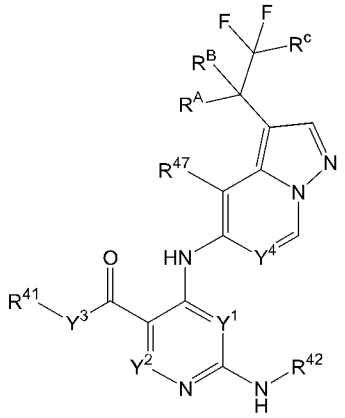
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[0018] 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 (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

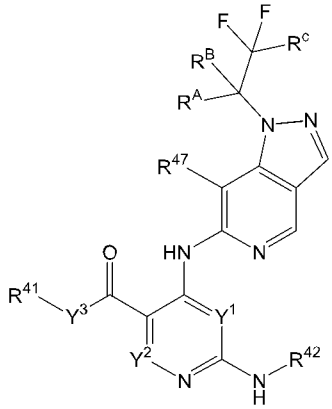
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[0019] 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 (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

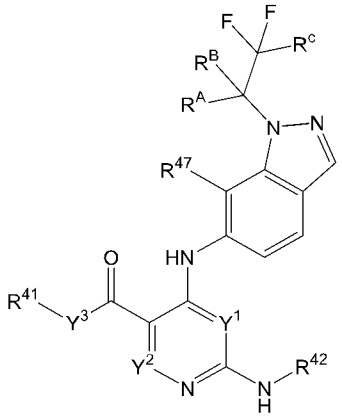
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[0020] 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 (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

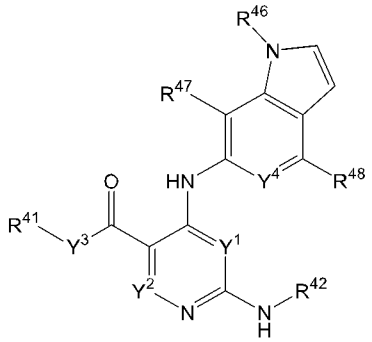
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[0021] 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 (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

R^{48} is H, halo or a C_1-C_3 alkyl,

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.

[0022] 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

[0023] 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.

[0024] The following terms, unless indicated otherwise according to the context wherein the terms are found, are intended to have the following meanings.

[0025] 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.

[0026] As used herein, “at least” a specific value is understood to be that value and all values greater than that value.

[0027] 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.

[0028] In this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference, unless the context clearly dictates otherwise.

[0029] 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.

[0030] Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive.

[0031] Any compositions or methods disclosed herein can be combined with one or more of any of the other compositions and methods provided herein.

[0032] 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.

[0033] 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.

[0034] 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.

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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, "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0039] 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)-.

[0040] 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).

[0041] 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.

[0042] 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.*, C_{1-10} 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 C_{1-6} 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, carbocyclylalkyl, 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.

[0043] 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.

[0044] 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, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R_a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tN(R^a)_2$ (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.

[0045] 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 C_{3-8} cycloalkyl radical. In some embodiments, “cycloalkyl” can be a C_{3-5} cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6) and the like. Examples of C_{3-7} carbocyclyl groups include norbornyl (C_7). Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-7} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-13} carbocyclyl groups include the aforementioned C_{3-8} 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.

[0046] 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.

[0047] As used herein, the term “heteroatom” refers to oxygen (O), nitrogen (N), sulfur (S), and phosphorus (P).

[0048] 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.*, C_{1-4} heteroalkyl, which refers to the chain length in total, which in this example is 4 atoms long. For example, a $-CH_2OCH_2CH_3$ radical is referred to as a "C_4" 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 ($-CH_2CH_2OCH_3$), ethoxymethanyl ($-CH_2OCH_2CH_3$), (methoxymethoxy)ethanyl ($-CH_2CH_2OCH_2OCH_3$), (methoxymethoxy) methanyl ($-CH_2OCH_2OCH_3$) and (methoxyethoxy)methanyl ($-CH_2OCH_2CH_2OCH_3$) and the like; amines such as ($-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2NHCH_2CH_3$, $-CH_2N(CH_2CH_3)(CH_3)$) and the like.

[0049] 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-pyranyl, 1,2,3,4-tetrahydropyridine, 3,4-dihydro-2H-[1,4]oxazine, etc.

[0050] 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.

[0051] 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).

[0052] "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.

[0053] 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, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno [2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 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, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, 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]pyrimdinyl, 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]pridinyl, 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, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R_a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tN(R^a)_2$ (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.

[0054] 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.

[0055] 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.*

[0056] 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.

[0057] 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).

[0058] 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.

[0059] 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).

[0060] 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.

[0061] 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.

[0062] 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).

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

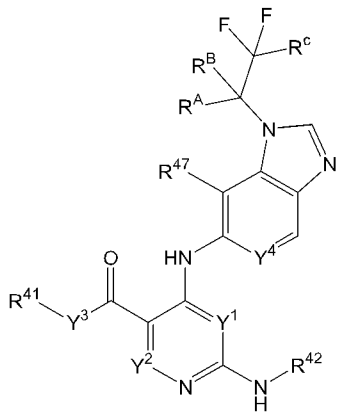
Detailed Description of the Invention

[0077] 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.

[0078] 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-a) by inhibiting TYK2-mediated signal transduction.

[0079] 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.

[0080] 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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

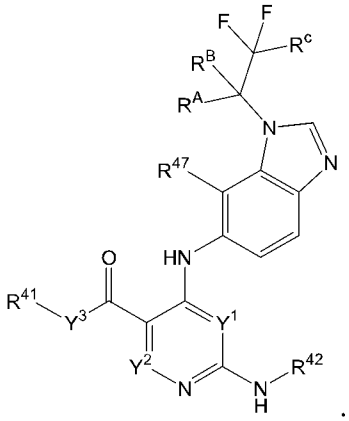
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

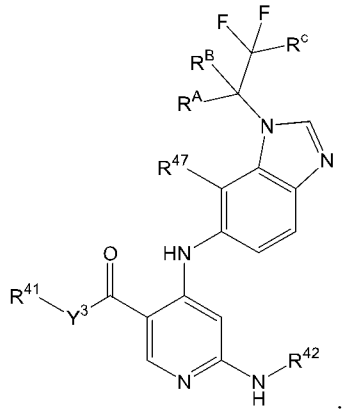
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[0081] In certain embodiments of (I), Y^4 is CH and the compound has the structure:



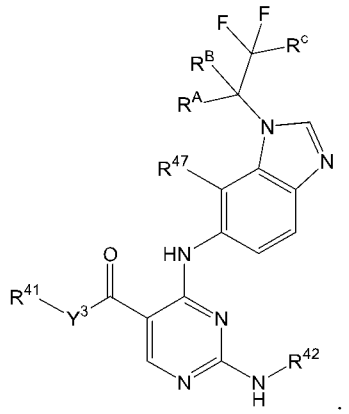
(I[a])

[0082] In certain embodiments of (I[a]), Y^1 is CH and Y^2 is CH, having the structure:



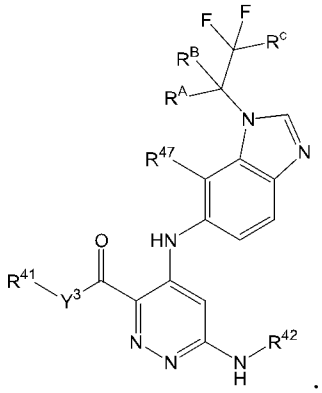
(I[b])

[0083] In certain embodiments of (I[a]), Y^1 is N and Y^2 is CH, having the structure:



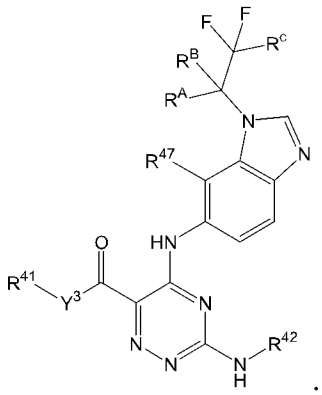
(I[c])

[0084] In certain embodiments of (I[a]), Y^1 is CH and Y^2 is N, having the structure:



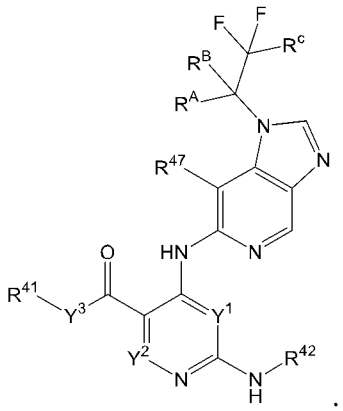
(I^6)

[0085] In certain embodiments of (I^a), Y^1 is N and Y^2 is N, having the structure:



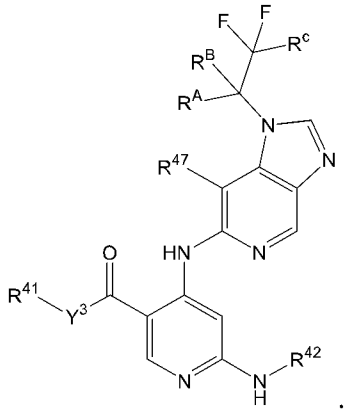
(I^c)

[0086] In certain embodiments of (I), Y^4 is N, having the structure:



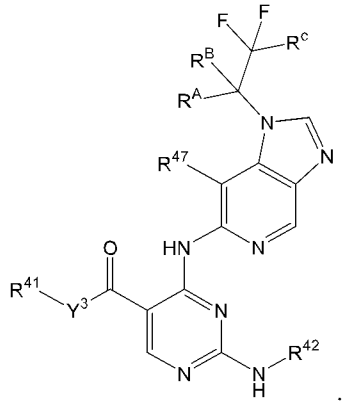
(I^f)

[0087] In certain embodiments of (I^f), Y^1 is CH and Y^2 is CH, having the structure:



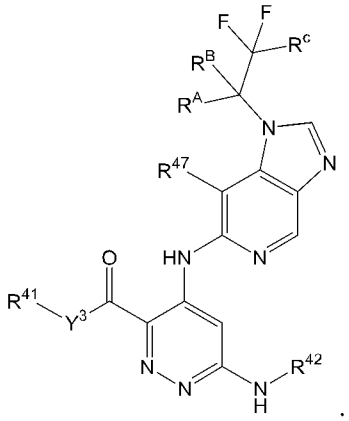
(I^g)

[0088] In certain embodiments of (I^f), Y^1 is N and Y^2 is CH, having the structure:



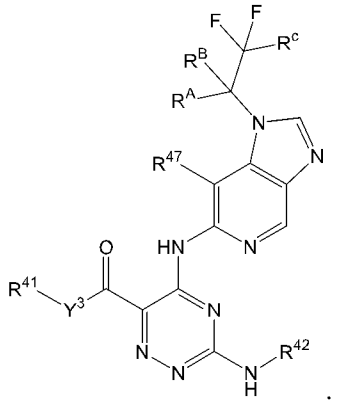
(I^h)

[0089] In certain embodiments of (I^f), Y^1 is CH and Y^2 is N, having the structure:



(I^i)

[0090] In certain embodiments of (I^f), Y^1 is N and Y^2 is N, having the structure:



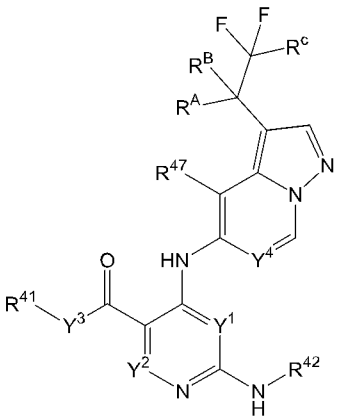
(I^j)

[0091] In certain embodiments of (I)-(I^j), R^A is H and R^B is H.

[0092] In certain embodiments of (I)-(I^j), R^C is CH_3.

[0093] In certain embodiments of (I)-(I^j), R^C is not CH_3.

[0094] In another aspect, the invention generally relates to a compound having the structural formula (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

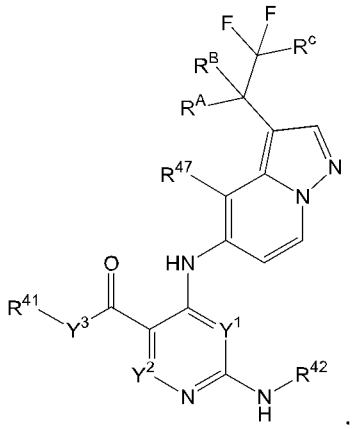
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

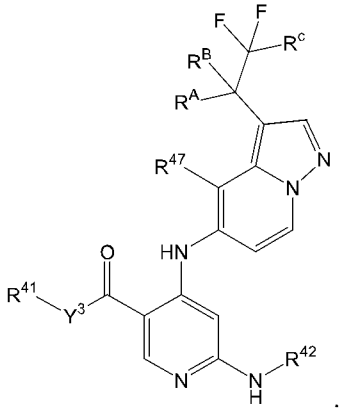
[0095] In certain embodiments of (II), Y^4 is CH, having the structure:



.

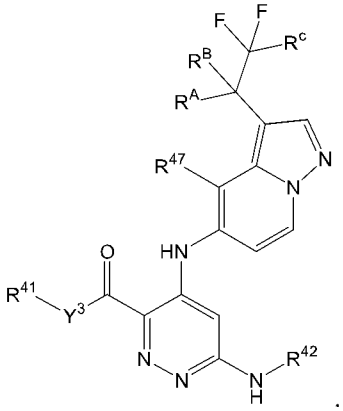
(II^a)

[0096] In certain embodiments of (II^a), Y^1 is CH and Y^2 is CH, having the structure:



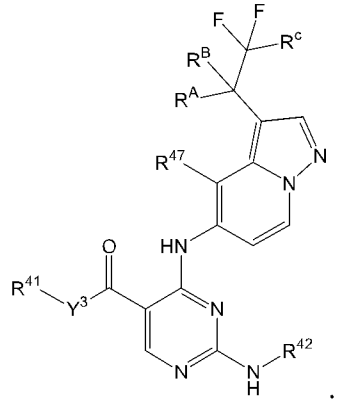
(II^b)

[0097] In certain embodiments of (II^a), Y^1 is CH and Y^2 is N, having the structure:



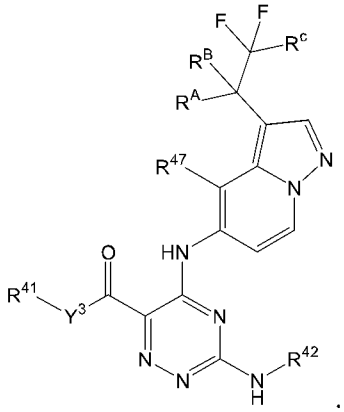
(II^c)

[0098] In certain embodiments of (II^a), Y^1 is N and Y^2 is CH, having the structure:



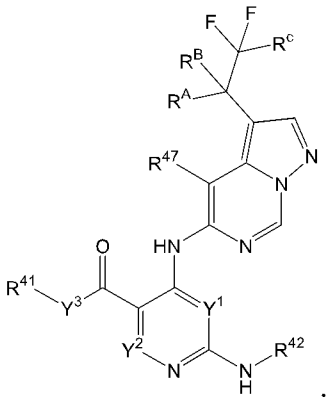
(II^d)

[0099] In certain embodiments of (II^a), Y^1 is N and Y^2 is N, having the structure:



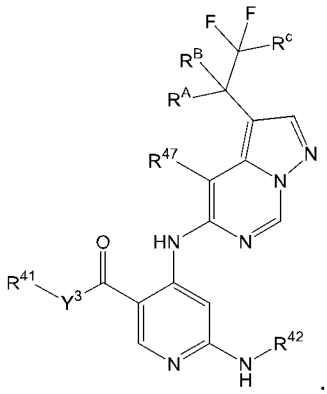
(II^c)

[00100] In certain embodiments of (II), Y^4 is N, having the structure:



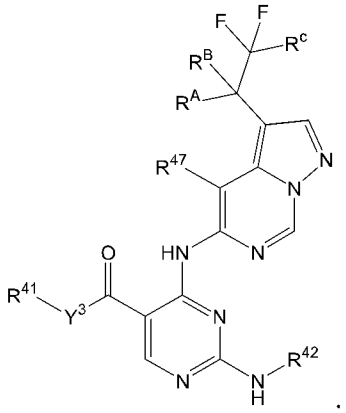
(II^f)

[00101] In certain embodiments of (II^f), Y^1 is CH and Y^2 is CH, having the structure:



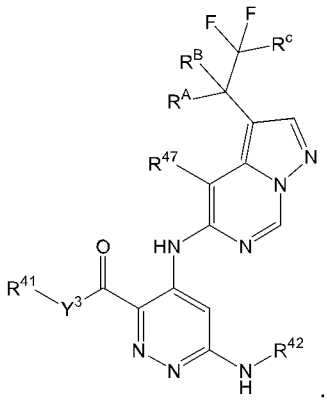
(II^g)

[00102] In certain embodiments of (II^f), Y^1 is N and Y^2 is CH, having the structure:



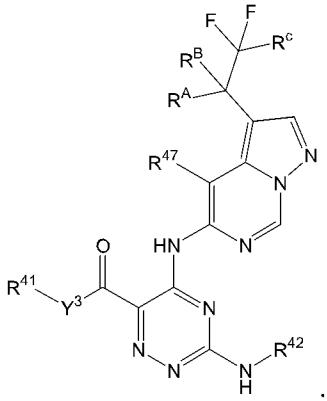
(II^h)

[00103] In certain embodiments of (II^f), Y^1 is CH and Y^2 is N, having the structure:



(II^i)

[00104] In certain embodiments of (II^f), Y^1 is N and Y^2 is N, having the structure:



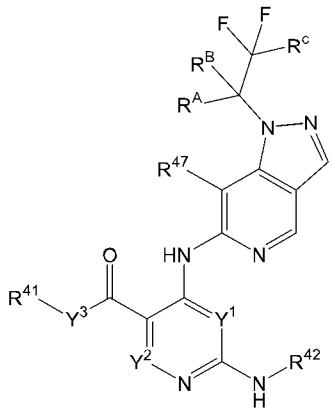
(II^j)

[00105] In certain embodiments of (II)-(II^j), R^A is H and R^B is H.

[00106] In certain embodiments of (II)-(II^j), R^C is CH_3.

[00107] In certain embodiments of (II)-(II^j), R^C is not CH_3.

[00108] In yet another aspect, the invention generally relates to a compound having the structural formula (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

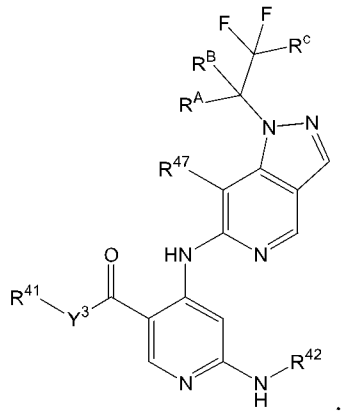
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

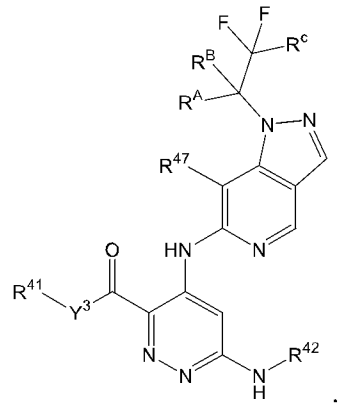
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[00109] In certain embodiments of (III), Y^1 is CH and Y^2 is CH, having the structure:



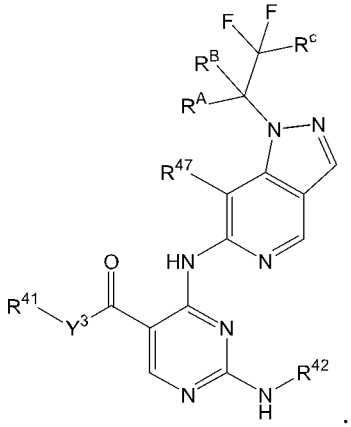
(III^a)

[00110] In certain embodiments of (III), Y^1 is CH and Y^2 is N, having the structure:



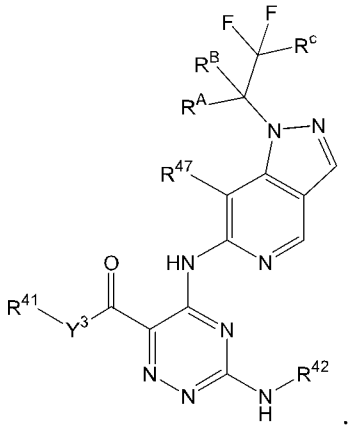
(III[b])

[00111] In certain embodiments of (III), Y^1 is N and Y^2 is CH, having the structure:



(III[c])

[00112] In certain embodiments of (III), Y^1 is N and Y^2 is N, having the structure:



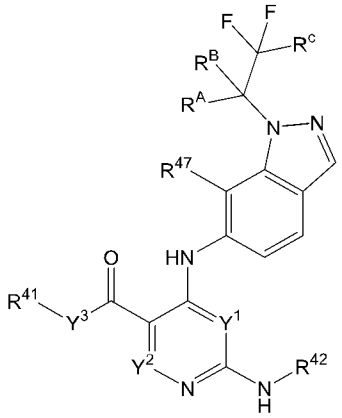
(III[d])

[00113] In certain embodiments of (III)-(III[d]), R^A is H and R^B is H.

[00114] In certain embodiments of (III)-(III[d]), one of R^A and R^B is not H.

[00115] In certain embodiments of (III)-(III[d]), R^C is not CH_3.

[00116] In yet another aspect, the invention generally relates to a compound having the structural formula (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

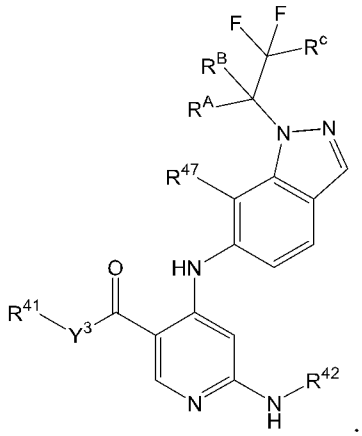
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

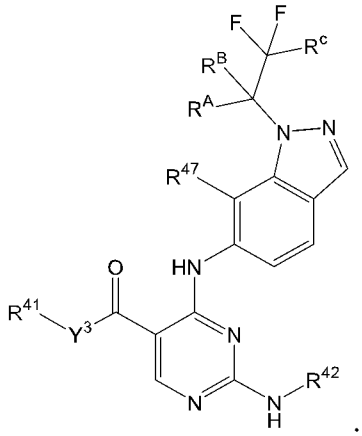
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

[00117] In certain embodiments of (IV), Y^1 is CH and Y^2 is CH, having the structure:



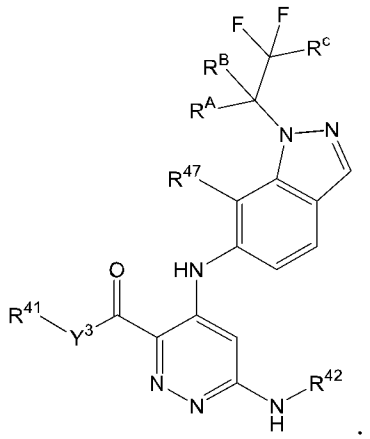
(IV^a)

[00118] In certain embodiments of (IV), Y^1 is N and Y^2 is CH, having the structure:



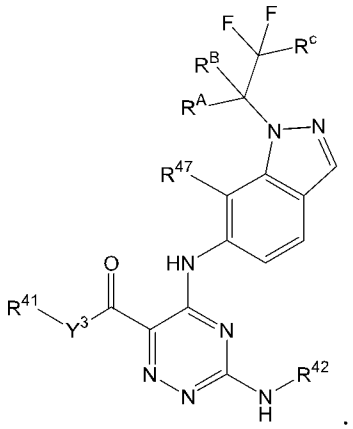
(IV^b)

[00119] In certain embodiments of (IV), Y^1 is CH and Y^2 is N, having the structure:



(IV^c)

[00120] In certain embodiments of (IV), Y^1 is N and Y^2 is N, having the structure:



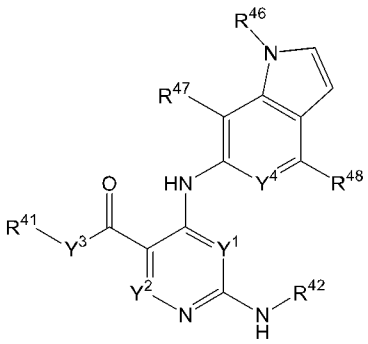
(IV^d)

[00121] In certain embodiments of (IV)-(IV^d), R^A is H and R^B is H.

[00122] In certain embodiments of (IV)-(IV^d), R^C is CH_3.

[00123] In certain embodiments of (IV)-(IV^d), R^C is not CH_3.

[00124] In yet another aspect, the invention generally relates to a compound having the structural formula (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

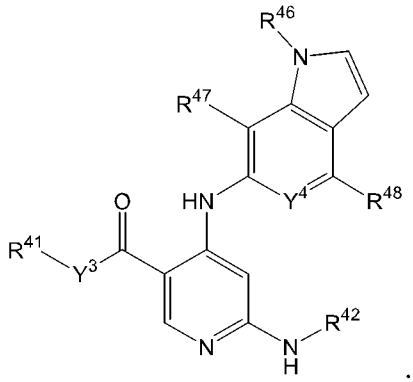
R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

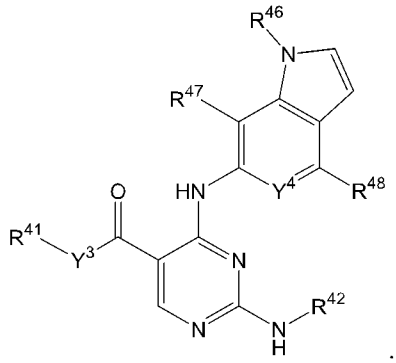
R^{48} is H, halo or a C_1-C_3 alkyl.

[00125] In certain embodiments of (V), Y^1 is CH and Y^2 is CH, having the structure:



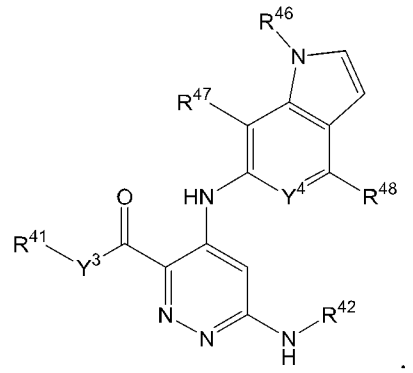
(V[a])

[00126] In certain embodiments of (V), Y^1 is N and Y^2 is CH, having the structure:



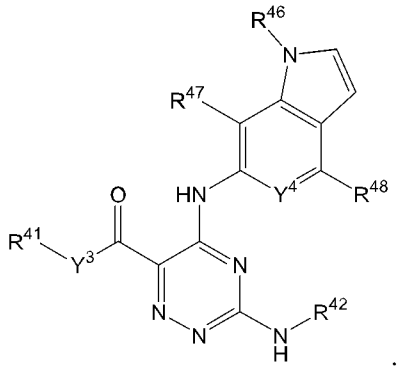
(V[b])

[00127] In certain embodiments of (V), Y^1 is CH and Y^2 is N, having the structure:



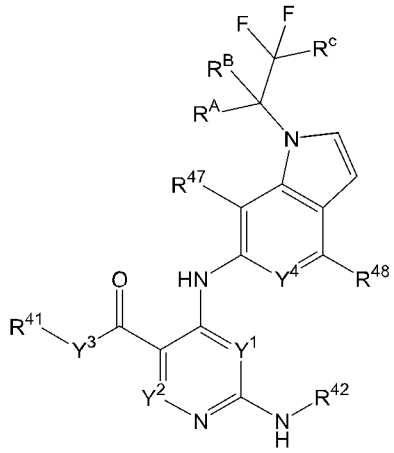
(V[c])

[00128] In certain embodiments of (V), Y^1 is N and Y^2 is N, having the structure:



(V^d)

[00129] In certain embodiments of (V), the compound has the structure:



(V^e)

wherein

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

[00130] In certain embodiments of (V)-(V^e), Y^4 is CH.

[00131] In certain embodiments of (V)-(V^e), Y^4 is N.

[00132] In certain embodiments of (V)-(V^e), R^{48} is H.

[00133] In certain embodiments of (V)-(V^e), R^{48} is halo.

[00134] In certain embodiments of (V^e), R^A is H and R^B is H.

[00135] In certain embodiments of (V^e), R^C is CH_3.

[00136] In certain embodiments of (V^e), R^C is not CH_3.

[00137] In certain embodiments of (I)-(V^e), R^{47} is C_1-C_3 alkoxy.

[00138] In certain embodiments of (I)-(V^e), R^{47} is OCH_3.

[00139] In certain embodiments of (I)-(V^e), R^{47} is OCD_3.

[00140] In certain embodiments of (I)-(V^e), Y^3 is NR.

[00141] In certain embodiments of (I)-(V^e), Y^3 is NH.

[00142] In certain embodiments of (I)-(V^e), Y^3 is O.

[00143] In certain embodiments of (I)-(V^e), Y^3 is O-NH.

[00144] In certain embodiments of (I)-(V^e), R^{41} is CH_3.

[00145] In certain embodiments of (I)-(V^e), R^{41} is CD_3.

[00146] In certain embodiments of (I)-(V^e), R^{42} is $R^{42'}$.

[00147] In certain embodiments of (I)-(V^e), R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is selected from C_1-C_6 alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{42c}.

[00148] In certain embodiments, R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is cyclopropyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.

[00149] In certain embodiments, R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is bis-spiro-cyclopropyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.

[00150] In certain embodiments, R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is cyclobutyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.

[00151] In certain embodiments, R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is C_1-C_6 alkyl, optionally substituted with one or more of F, Cl, CH_3, CF_3, CN, NRR' and OR.

[00152] In certain embodiments of (I)-(V^e), R^{42} is $(C=O)NHR^{42b}$, wherein R^{42b} is selected from C_1-C_6 alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{42c}.

[00153] In certain embodiments of (I)-(V^e), R^{42} is phenyl substituted with 0-2 R^{42c}.

[00154] In certain embodiments of (I)-(V^e), R^{42} is pyridinyl substituted with 0-2 R^{42c}.

[00155] In certain embodiments of (I)-(V^e), R^{42} is pyrazolyl substituted with 0-2 R^{42c}.

[00156] In certain embodiments of (I)-(V^e), R^{42} is pyrimidyl substituted with 0-2 R^{42c}.

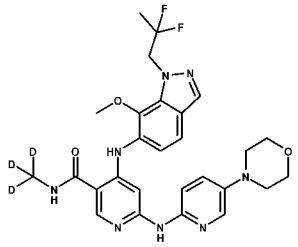
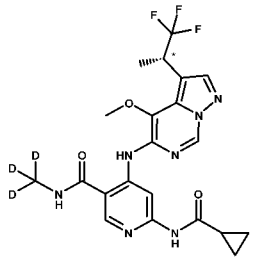
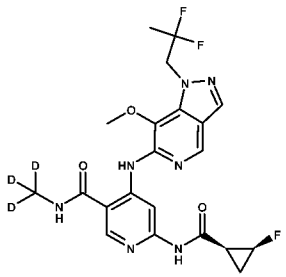
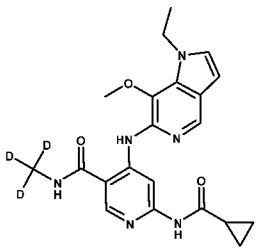
[00157] In certain embodiments, R^{42c} is CH_3 or CD_3.

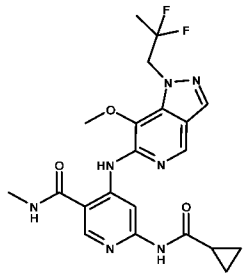
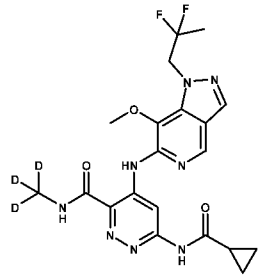
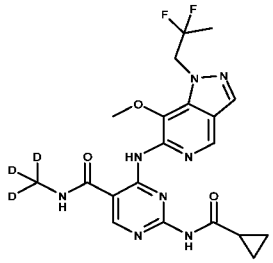
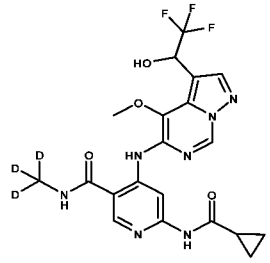
[00158] In certain embodiments, R^{42c} is F.

[00159] Non-limiting examples of compounds of the invention include those listed in **Table 1A** in the Examples section herein, or a pharmaceutically acceptable form or an isotope derivative thereof.

[00160] In certain embodiments, a compound of the invention is selected from those listed in **Table 1B**, or a pharmaceutically acceptable form or an isotope derivative thereof.

Table 1B

Example	Structure	Name
4		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-indazol-6-yl)amino)-N-(methyl-d3)-6-((5-morpholinopyridin-2-yl)amino)nicotinamide
5B		(S*)6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide
8		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d3)nicotinamide
18		6-(Cyclopropanecarboxamido)-4-((1-ethyl-7-methoxy-1H-pyrrolo[3,2-c] pyridin-6-yl) amino)-N-(methyl-d3)nicotinamide

23		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-methylnicotinamide
24		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide
28		2-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide
30		6-(cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide

[00161] 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.

[00162] 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.

[00163] In certain embodiments, the pharmaceutical composition is suitable for oral administration.

[00164] In certain embodiments, the pharmaceutical composition is suitable for topical administration.

[00165] In certain embodiments, the pharmaceutical composition is suitable for GI-restricted administration.

[00166] 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.

[00167] In certain embodiments, the disease or disorder is an inflammatory disease.

[00168] In certain embodiments, the disease or disorder is an immune-mediated disease.

[00169] In certain embodiments, the disease or disorder is cancer.

[00170] 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.

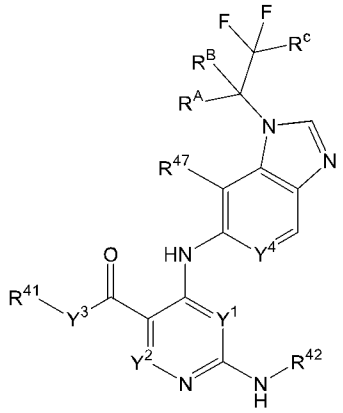
[00171] In yet another aspect, the invention generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[00172] In certain embodiments, the unit dosage form is a tablet.

[00173] In certain embodiments, the unit dosage form is a capsule.

[00174] In certain embodiments, the unit dosage form is a topical formulation.

[00175] 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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

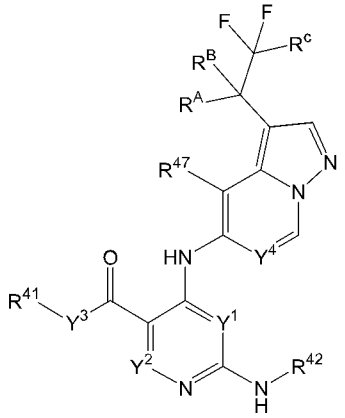
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[00176] 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 (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

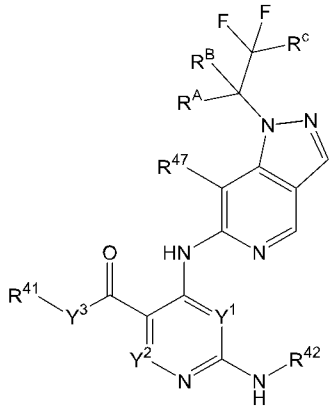
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[00177] 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 (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

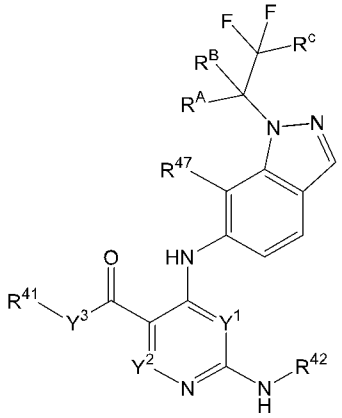
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[00178] 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 (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

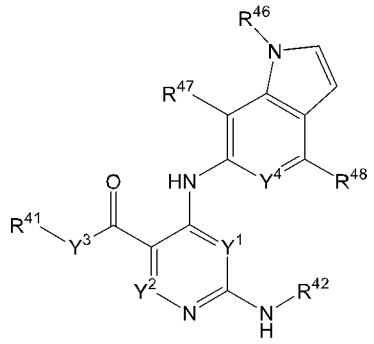
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

[00179] 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 (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

R^{48} is H, halo or a C_1-C_3 alkyl,

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.

[00180] In certain embodiments, the disease or disorder is an inflammatory disease.

[00181] In certain embodiments, the disease or disorder is an immune-mediated disease.

[00182] In certain embodiments, the disease or disorder is cancer.

[00183] 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.

In certain embodiments, administration is via oral administration.

In certain embodiments, administration is via topical administration.

In certain embodiments, administration is via GI-restricted administration.

[00184] 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.

[00185] In certain embodiments of the use, the disease or disorder is one or more of inflammatory diseases, immune-mediated diseases and cancer.

[00186] In certain embodiments of the use, the disease or disorder is an inflammatory disease.

[00187] In certain embodiments of the use, the disease or disorder is an immune-mediated disease.

[00188] In certain embodiments of the use, the disease or disorder is cancer.

[00189] In certain embodiments of the use, the medicament is for oral administration.

[00190] In certain embodiments of the use, the medicament is for topical administration.

[00191] In certain embodiments of the use, the medicament is for GI restriction administration.

[00192] 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.

[00193] 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.

[00194] 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 ostomyelitis, Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans 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, Parsonnage-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.

[00195] 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 erthematosus, 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 (GVDH).

[00196] 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.

[00197] 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.

[00198] 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 ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[00199] By isotopically-labeling the presently disclosed compounds, the compounds may be useful in drug and/or substrate tissue distribution assays. Tritiated (^{3}H) 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 (^{2}H) 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.

[00200] Further, substitution of normally abundant hydrogen (^{1}H) 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.)

[00201] 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.

[00202] 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.

[00203] 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.

[00204] 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, alignates, 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.

[00205] 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.

[00206] 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.

[00207] 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/EA

Acetonitrile:	ACN or MeCN
Isopropanol:	IPA
Triethylamine:	TEA
Tetrahydrofuran:	THF
Sodium hydroxide:	NaOH
Propylphosphonic Acid Anhydride:	T_3P
Nitrogen:	N_2
N,*N*-Diisopropylethylamine:	DIPEA
N, *N*-Dimethylformamide:	DMF
4-Methylbenzenesulfonic acid:	pTSA or TsOH
N,*N*-Dimethylformamide dimethyl acetal:	DMF-DMA
N-Iodosuccinimide:	NIS
Lithium bis(trimethylsilyl)amide:	LiHMDS
2-(Trimethylsilyl)ethoxymethyl chloride:	SEMCl
2,4-Dimethoxybenzylamine:	$DMBNH_2$
4-Methoxybenzylamine:	$PMBNH_2$
2,2,6,6-Tetramethylpiperidinooxy:	TEMPO
Thin-Layer Chromatography:	TLC
High Performance Liquid Chromatography:	HPLC
Room temperature:	r.t.
Hours:	h

[00208] Representative methods of *prep*-HPLC: Flow rate and gradient may change.

[00209] Exemplary methods for *prep*-HPLC are provided below.

[00210] Method A: NH_4HCO_3: Column: Gilson2-Xbridge C18 19*150 mm, 5 μm; mobile phase: CH_3CN in water (0.1% NH_4HCO_3) from 20% to 60%, flow rate: 15 mL/min.

[00211] Method B: TFA: Column: Waters-Xbridge C18 10*190 mm, 5 μm; mobile phase: CH_3CN in water (0.1% TFA) from 15% to 40%, flow rate: 15 mL/min.

[00212] Method C: HCOOH: Column: Waters-Xbridge C18 10*190 mm, 5 μm; mobile phase: CH_3CN in water (0.1% formic acid) from 15% to 40%, flow rate: 15 mL/min.

[00213] Method D: HCOOH: Column: Waters SunFire ® Prep C18 OBDTM (5 micron, 19*150 mm); mobile phase: CH_3CN in water (0.1% formic acid) from 18% to 38%, flow rate: 20

mL/min.

[00214] Method E: NH_4HCO_3: Column: Waters Xbridge ® Prep C18 OBD™ (5 micron, 19*150 mm); mobile phase: CH_3CN in water (10 mM NH_4HCO_3) from 20% to 60%, flow rate: 20 mL/min.

[00215] Method F: HCOOH: Columns: Waters Atlantis T3 19*150 mm, 5 μm; mobile phase: CH_3CN in H_2O (0.1% formic acid) from 16% to 30%, flow rate: 20 mL/min.

Representative methods of chiral *prep*-HPLC:

[00216] Method G: Gilson 281, Daicel Chiralpak IB N, 10 μm 30*250 mm; Mobile phase: Hexane/EtOH = 60/40, Flow rate: 25 mL/min.

[00217] Method H: Gilson 281, Daicel Chiralpak IB N, 10 μm 30*250 mm; Mobile phase: Hexane/EtOH = 50/50, Flow rate: 25 mL/min.

Representative methods of analytical-HPLC:

[00218] 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% NH_4OAc) 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.

[00219] 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.

[00220] 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% NH_4OAc) 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.

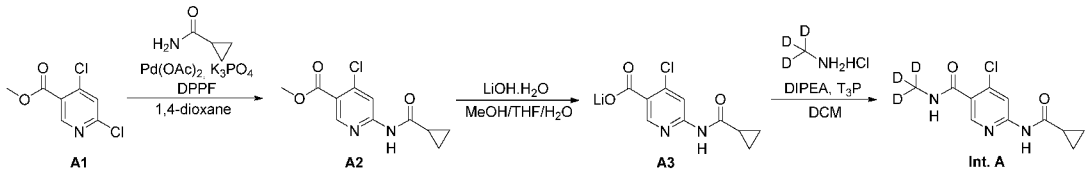
[00221] Method 4: Analysis was performed on an Agilent 1260_series HPLC-6125C MS. HPLC Long Gradient Equivalent 20% to 100% acetonitrile in water (containing 0.1% formic acid) run time of 6 minutes with a flow rate of 0.8 mL/min. Agilent ZORBAX SB-C18 column (1.8 micron, 2.1*50 mm) was used at a temperature of 30 °C.

[00222] Method 5: Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/EtOH (60/40) run time of 20 minutes with a flow rate of 1 mL/min.

CHIRALPAK IB N-5 (5 um, 4.6*250 mm) was used at a temperature of 30 °C.

[00223] Method 6: Analysis was performed on a SHIMADZU 20A HPLC. HPLC Long Gradient Equivalent Hexane/EtOH (50/50) run time of 20 minutes with a flow rate of 1 mL/min. CHIRALPAK IB N-5 (5 um, 4.6*250 mm) was used at a temperature of 30 °C.

Intermediate A



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

[00224] A mixture of **A1** (2.0 g, 9.71 mmol), cyclopropanecarboxamide (826 mg, 9.71 mmol), $Pd(OAc)_2$ (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 chromagraphy (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 $(M+H)^+$ = 255.0.

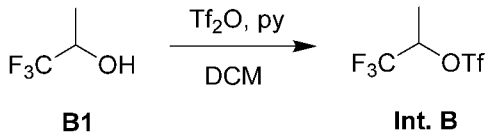
Step 2. Lithium 4-chloro-6-(cyclopropanecarboxamido)nicotinate (A3)

[00225] 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 $LiOH.H_2O$ (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 $(M+H)^+$ = 241.1.

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

[00226] 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.

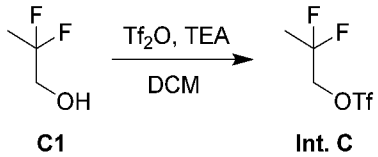
Intermediate B



Step 1. 1,1,1-Trifluoropropan-2-yl trifluoromethanesulfonate (Int. B)

[00227] To a solution of **B1** (1.24 g, 10.87 mmol) and pyridine (1.12 g, 14.13 mmol, 1.14 mL) in DCM (10 mL) was added trifluoromethanesulfonic anhydride (3.37 g, 11.96 mmol, 2.01 mL) at 0 °C, then the mixture was stirred at r.t. for 2 h. The mixture was filtered, The filter cake was rinsed with DCM (17 mL) to yield the compound **Int. B** (27 mL, 10.87 mmol, 0.4 M in DCM, yield given) as a solution, which was directly used in the next step.

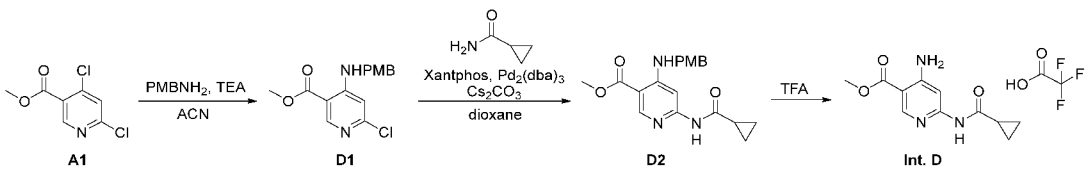
Intermediate C



Step 1. 2,2-Difluoropropyl trifluoromethanesulfonate (Int. C)

[00228] To a solution of **C1** (1 g, 10.4 mmol) and triethylamine (1.5 g, 15.6 mmol) in DCM (15 mL) was added trifluoromethanesulfonic anhydride (4.4 g, 15.6 mmol) dropwise at -20 °C. The reation was stirred at -20 °C for 16 h and diluted with DCM (10 mL). The mixture was washed with ice water (10 mL). The separated organic layer was washed with 20% Na_2CO_3 aqueous solution (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to afford **Int. C** (2.3 g, 97% yield) as a black oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.08 (t, J = 13.6 Hz, 2H), 1.72 (t, J = 19.2 Hz, 3H).

Intermediate D



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

[00229] 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 H_2O (100 mL), extracted with EA (50 mL*3), washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromtography (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.

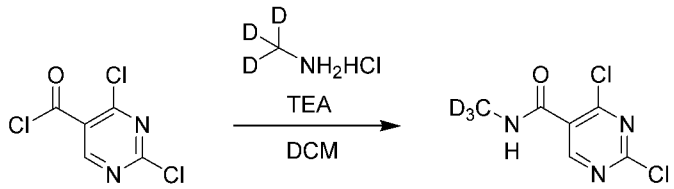
Step 2. Methyl 6-(cyclopropanecarboxamido)-4-((4-methoxybenzyl)amino)nicotinate (D2)

[00230] A mixture of **D1** (2 g, 6.52 mmol), cyclopropanecarboxamide (1.11 g, 13.04 mmol), XantPhos (754 mg, 1.30 mmol), $Pd_2(dba)_3$ (597 mg, 0.65 mmol), Cs_2CO_3 (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 H_2O (100 mL), extracted with EA (60 mL*3), washed with brine, dried over Na_2SO_4 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)

[00231] 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



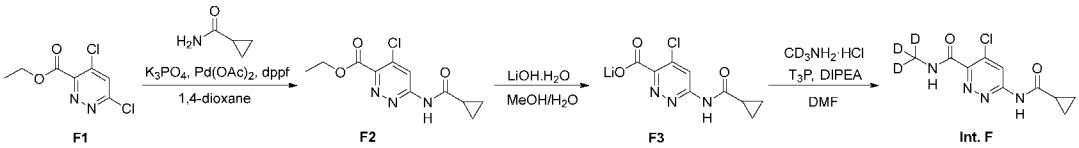
E1 **Int. E**

Step 1. 2,4-Dichloro-*N*-(methyl-d_3)pyrimidine-5-carboxamide (Int. E)

[00232] 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. ^{1}H 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-(cyclopropanecarboxamido)pyridazine-3-carboxylate (F2)

[00233] To a solution of **F1** (500 mg, 2.4 mmol) and cyclopropanecarboxamide (408 mg, 4.8 mmol) in 1,4-dioxane (20 mL) was added $Pd(OAc)_2$ (54 mg, 0.24 mmol), dppf (265 mg, 0.48 mmol) and K_3PO_4 (1.01 g, 4.8 mmol), then the mixture was stirred at 90 °C for 4 h under N_2 atmosphere. The mixture was diluted with H_2O (50 mL), extracted with EtOAc (30 mL*3), washed with brine (30 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 10/1) to get compound **F2** (200 mg, 33% yield) as an off-white solid. LC-MS (ESI, Method 4) t_R = 3.46 min, m/z $(M+H)^+$ = 270.1.

Step 2. Lithium 4-chloro-6-(cyclopropanecarboxamido)pyridazine-3-carboxylate (F3)

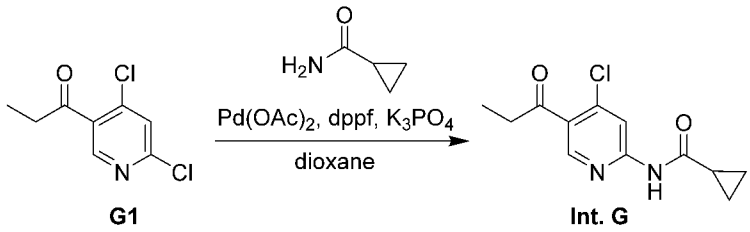
[00234] To a solution of **F2** (100 mg, 0.41 mmol) in MeOH (1 mL) and H_2O (1 mL) was added $LiOH.H_2O$ (34 mg, 0.82 mmol), then the mxiture was stirred at r.t. for 2 h. The reaction mixture was concentrated to get **F3** (132 mg, crude) and used for the next step directly without futher purification. LC-MS (ESI, Method 4) t_R = 1.44 min, m/z $(M+H)^+$ = 242.1.

Step 3. 4-Chloro-6-(cyclopropanecarboxamido)-*N*-(methyl-d_3)pyridazine-3-carboxamide (Int. F)

[00235] To a solution of **F3** (132 mg, crude) in DMF (1 mL) was added methan-d_3-amine hydrochloride (58 mg, 0.82 mmol) and DIPEA (251 mg ,1.95mmol), the mixture was stirred at r.t. for 20 min, then T_3P (368 mg, 0.58 mmol, 50% in EtOAc) was added to the reaction mixture, the reaction mixture was stirred at r.t. for 3 h. The mixture was diluted with H_2O (50 mL), extracted with EtOAc (30 mL*3), washed with brine (30 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 10/1) to get compound **Int. F** (15

mg, 14% yield, over two steps) as an off-white solid. LC-MS (ESI, Method 4) t_R = 2.24 min, m/z $(M+H)^+$ = 258.1.

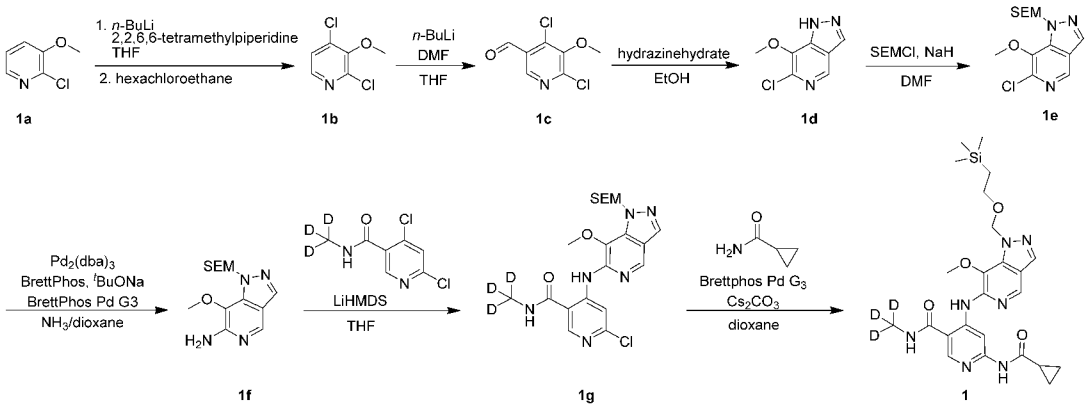
Intermediate G



Step 1. *N*-(4-chloro-5-propionylpyridin-2-yl)cyclopropanecarboxamide (Int. G)

[00236] A mixture of 1-(4,6-dichloropyridin-3-yl)propan-1-one (170 mg, 0.83 mmol, CAS 66525-49-1), cyclopropanecarboxamide (85 mg, 0.99 mmol), dppf (23 mg, 0.042 mmol), $Pd(OAc)_2$ (19 mg, 0.042 mmol) and K_3PO_4 (265 mg, 1.25 mmol) in dioxane (3 mL) was stirred at 90 °C for 3 h under N_2 atmosphere. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **Int. G** (140 mg, 67% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.34 (s, 1H), 8.30 (brs, 1H), 2.99 (q, J = 7.2 Hz, 2H), 1.60-1.53 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H), 1.16-1.12 (m, 2H), 0.98-0.93 (m, 2H).

Example 1



Step 1. 2,4-Dichloro-3-methoxypyridine (1b)

[00237] To a solution of *n*-BuLi (5.5 mL, 13.93 mmol, 2.5 M in THF) in THF (25 mL) was added 2,2,6,6-tetramethylpiperidine (2.3 g, 16.72 mmol) at -78 °C. The reaction mixture was

stirred at -78 °C for 15 min. Then to the reaction mixture was added a solution of **1a** (2.0 g, 13.93 mmol) in THF (25 mL). The reaction mixture was stirred at -78 °C for 4 h. A solution of hexachloroethane (6.6 g, 27.86 mmol) in THF (50 mL) was added dropwise to the reaction and the temperature was kept below -60 °C. After stirring for another 2 h at -78 °C, the reaction mixture was quenched with *sat.* NH_4Cl (20 mL), diluted with water (40 mL) and extracted with EtOAc (30 mL*3). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to afford compound **1b** (700 mg, 28% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 5.6 Hz, 1H), 3.95 (s, 3H).

Step 2. 4,6-Dichloro-5-methoxynicotinaldehyde (1c)

[00238] To a solution of *n*-BuLi (9.4 mL, 23.59 mmol, 2.5 M in THF) in THF (30 mL) was added **1b** (2.8 g, 15.73 mmol) at -78 °C. After stirring at -78 °C for 30 min, to the reaction mixture was added anhydrous DMF (1.7 g, 23.59 mmol) at -78 °C. After stirring for 2 h at -78 °C, the reaction was quenched with *sat.* NH_4Cl (20 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to afford compound **1c** (2.0 g, 61% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.60 (s, 1H), 3.93 (s, 3H).

Step 3. 6-Chloro-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridine (1d)

[00239] A mixture of **1c** (1.5 g, 7.28 mmol) and hydrazine hydrate (3.6 g, 21.84 mmol, 30% wt in water) in EtOH (20 mL) was stirred at 100 °C for 8 h. The reaction mixture was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford compound **1d** (300 mg, 22% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 13.95 (s, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 4.04 (s, 3H).

Step 4. 6-Chloro-7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*c*]pyridine (1e)

[00240] To a mixture of **1d** (3 g, 16.34 mmol) in DMF (50 mL) was added NaH (1.3 g, 32.68 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 30 min and to it was added SEMCl (4 g, 24.51 mmol) at 0 °C. After stirring at 10 °C for 1 h, the reaction was

quenched with H_2O (50 mL) and extracted with EtOAc (50 mL). The separated organic layer was washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 3/1) to afford **1e** (1.7 g, 33% yield) as a yellow oil. LC-MS (ESI, Method 3) t_R = 1.88 min, m/z $(M+H)^+$ = 314.1.

Step 5. 7-Methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-amine (1f)

[00241] A mixture of **1e** (1.7 g, 5.42 mmol), $Pd_2(dba)_3$ (248 mg, 0.27 mmol), BrettPhos (145 mg, 0.27 mmol), ^{t}BuONa (780 mg, 8.12 mmol) and *sat.* NH_3/dioxane (20 mL) was stirred at 100 °C for 12 h under N_2 atmosphere. The mixture was cooled and concentrated. The residue was purified by *prep*-HPLC (Method A) to afford **1f** (550 mg, 34% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 1.69 min, m/z $(M+H)^+$ = 295.2.

Step 6. 6-Chloro-4-((7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (1g)

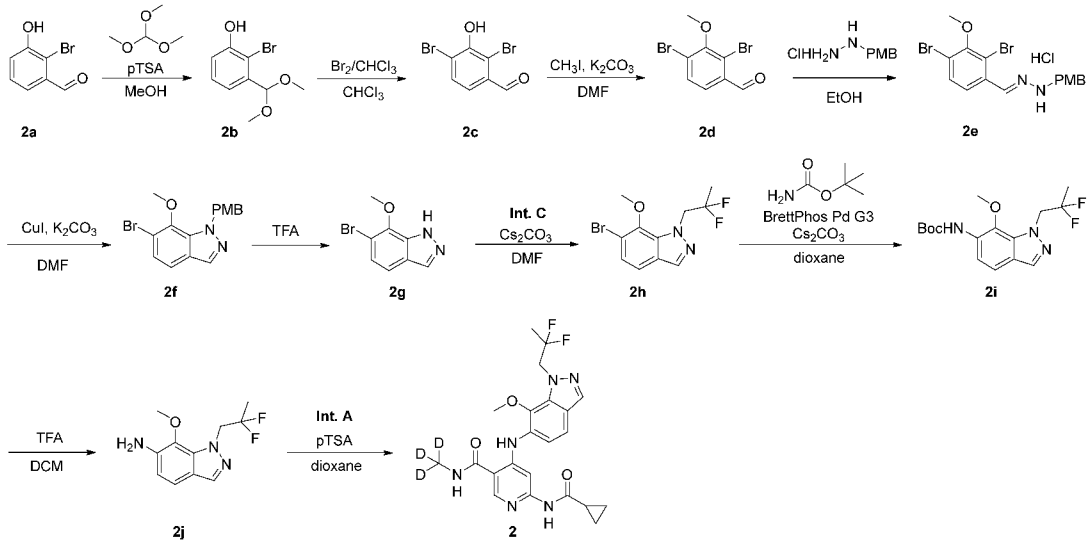
[00242] To a solution of **1f** (500 mg, 1.70 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (389 mg, 1.87 mmol) in THF (5 mL) was added LiHMDS (6.79 mL, 6.79 mmol, 1 M in THF) at -10 °C. The reaction was stirred at -10 °C to r.t. for 1 h and quenched with ice-water (20 mL). The resultant mixture was extracted with EtOAc (30 mL*2) and the combined organic layer was concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 97/3) to afford **1g** (610 mg, 77% yield) as a brown solid. LC-MS (ESI, Method 3) t_R = 1.45 min, m/z $(M+H)^+$ = 466.3.

Step 7. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (1)

[00243] A mixture of **1g** (600 mg, 1.29 mmol), cyclopropanecarboxamide (548 mg, 6.44 mmol), BrettPhos Pd G3 (233 mg, 0.26 mmol) and Cs_2CO_3 (839 mg, 2.57 mmol) in 1,4-dioxane (6 mL) was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford **1** (200 mg, 30% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 10.79 (s, 1H), 9.37 (s, 1H), 8.76 (s, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 5.86 (s, 2H), 4.00 (s, 3H), 3.69 (t, J = 8.4 Hz, 2H), 2.12-2.07 (m, 1H), 0.97-0.87 (m, 6H), 0.03 (s, 9H).

LC-MS (ESI, Method 2) t_R = 4.13 min, m/z $(M+H)^+$ = 515.1.

Example 2



Step 1. 2-Bromo-3-(dimethoxymethyl)phenol (2b)

[00244] To a solution of **2a** (2 g, 9.95 mmol) and trimethoxymethane (5.28 g, 49.75 mmol, 5.45 mL) in MeOH (30 mL) was added pTSA (172 mg, 1.00 mmol). The mixture was stirred at 100 °C for 16 h. The solvent was removed under vacuum to give crude product **2b** (2.5 g, yield given) as a yellow oil. LC-MS (ESI, Method 4) t_R = 3.54 min, m/z (^{79}Br, M+H-32)$^+$ = 215.0.

Step 2. 2,4-Dibromo-3-hydroxybenzaldehyde (2c)

[00245] To a solution of **2b** (500 mg, 2.02 mmol) in $CHCl_3$ (5 mL) was added a solution of molecular bromine (323 mg, 2.02 mmol) in $CHCl_3$ (5 mL) at 0 °C. The reaction was stirred at 25 °C for 16 h. The reaction was quenched by *aq.* $Na_2S_2O_3$ (40 mL) and extracted with EtOAc (25 mL*3). The combined organic layer was washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1 to 3/1) to give the title compound **2c** (300 mg, 53% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 10.17 (d, J = 0.8 Hz, 1H), 7.83-7.65 (m, 1H), 7.27 (d, J = 8.4 Hz, 1H). LC-MS (ESI, Method 4) t_R = 2.92 min, m/z $(M+H)^+$ = 280.9.

Step 3. 2,4-Dibromo-3-methoxybenzaldehyde (2d)

[00246] To a solution of **2c** (300 mg, 1.07 mmol) and K_2CO_3 (296 mg, 2.14 mmol) in DMF (3

mL) was added iodomethane (228 mg, 1.61 mmol). The mixture was stirred at 25 °C for 2 h, then poured into water (20 mL) and extracted with EtOAc (20 mL*3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give the title product **2d** (300 mg, 95% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 4.00 min, m/z $(M+H)^+$ = 294.9.

Step 4. (*E*)-1-(2,4-dibromo-3-methoxybenzylidene)-2-(4-methoxybenzyl)hydrazine hydrochloride (2e)

[00247] Compound **2d** (3.0 g, 10.21 mmol) and (4-methoxybenzyl)hydrazine hydrochloride (2.12 g, 11.23 mmol) were dissolved in EtOH (30 mL). The resulting mixture was stirred at 25 °C for 16 h and then cooled to 0 °C. The cloudy mixture was filtered and washed with EtOH (5 mL) to afford the title compound **2e** (3.5 g, 74% yield) as a pale yellow solid. LC-MS (ESI, Method 4) t_R = 5.22 min, m/z $(M+H)^+$ = 427.0.

Step 5. 6-Bromo-7-methoxy-1-(4-methoxybenzyl)-1*H*-indazole (2f)

[00248] To a solution of **2e** (3.5 g, 7.53 mmol) in DMF (50 mL) was added K_2CO_3 (2.6 g, 18.83 mmol) and CuI (143 mg, 0.75 mmol). The mixture was stirred at 100 °C for 16 h. Water (200 mL) was added to above mixture. The solution was extracted with EtOAc (60 mL*3). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give crude compound **2f** (2.4 g, 91% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 4.81 min, m/z (^{79}Br, $M+H)^+$ = 347.1.

Step 6. 6-Bromo-7-methoxy-1*H*-indazole (2g)

[00249] **2f** (2.4 g, 6.91 mmol) was dissloved in TFA (20 mL), then the mixture was stirred at 90 °C for 4 h. Then the mixture was concentrated and diluted with H_2O (50 mL), adjusted pH to 7 with *aq.* $NaHCO_3$, then extracted with EtOAc (50 mL*3), washed with brine (50 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA = 1/1 to 1/10) to get the compound **2g** (1.4 g, 89% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 3.39 min, m/z (^{79}Br, $M+H)^+$ = 226.9.

Step 7. 6-Bromo-1-(2,2-difluoropropyl)-7-methoxy-1*H*-indazole (2h)

[00250] To a solution of **2g** (400 mg, 1.76 mmol) in DMF (5 mL) was added Cs_2CO_3 (1.15 g, 3.52 mmol) and **Int. C** (804 mg, 3.52 mmol). Then the mixture was stirred at r.t. for 2 h. The

mixture was diluted with H_2O (20 mL), extracted with EtOAc (20 mL*3), washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA = 20/1 to 1/1) to get the compound **2h** (100 mg, 19% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 4.95 (t, *J* = 13.2 Hz, 2H), 4.05 (s, 3H), 1.66 (t, *J* = 15.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 3.16 min, m/z (^{79}Br, M+H)$^+$ = 305.1.

Step 8. *Tert*-butyl (1-(2,2-difluoropropyl)-7-methoxy-1*H*-indazol-6-yl)carbamate (2i)

[00251] A mixture of **2h** (100 mg, 0.33 mmol), *tert*-butyl carbamate (77 mg, 0.66 mmol), Cs_2CO_3 (267 mg, 0.82 mmol), BrettPhos Pd G3 (30 mg, 0.033 mmol) in dioxane (2 mL) was stirred at 100 °C for 16 h. Then the mixture was concentrated, diluted with EtOAc, filtered and the filtrate was concentrated to get the crude compound **2i** (110 mg, 98% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 3.14 min, m/z (M+H)$^+$ = 342.2.

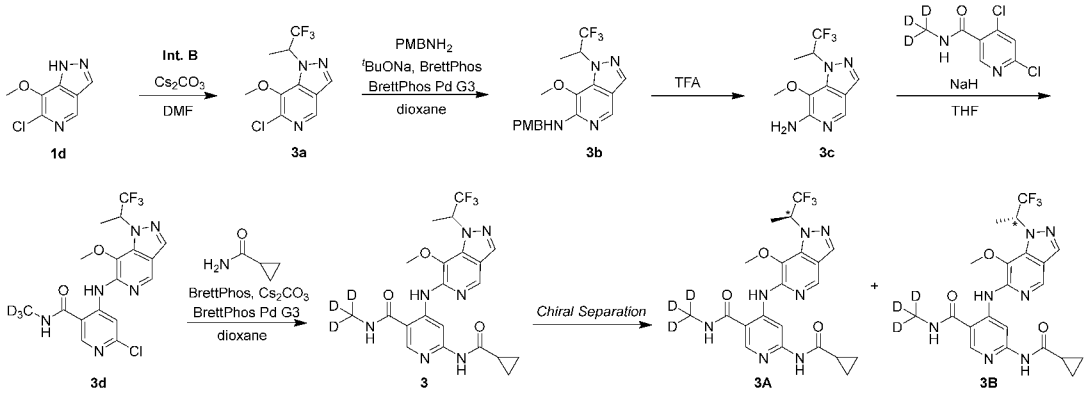
Step 9. 1-(2,2-Difluoropropyl)-7-methoxy-1*H*-indazol-6-amine (2j)

[00252] To a solution of **2i** (110 mg, 0.32 mmol) in DCM (2 mL) was added TFA (1 mL) at r.t., then the mixture was cocnentrated and diluted with H_2O (20 mL), basified to pH > 7 with *aq.* Na_2CO_3, extracted with EtOAc (20 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (EA in PE is 0% to 45%) to get compound **2j** (70 mg, 90% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 2.05 min, m/z (M+H)$^+$ = 242.1.

Step 4. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-*d*$_3$)nicotinamide (2)

[00253] To a solution of **2j** (40 mg, 0.17 mmol) and **Int. A** (47 mg, 0.18 mmol) in dioxane (1.5 mL) was added pTSA (29 mg, 0.17 mmol), then the mixture was stirred at r.t. for 16 h. The mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **2** (43.3 mg, 57% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 10.55 (s, 1H), 8.63 (s, 1H), 8.53 (s, 1H), 8.15 (s, 1H), 7.83 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 4.97 (t, *J* = 13.2 Hz, 2H), 3.78 (s, 3H), 1.96-1.91 (m, 1H), 1.65 (t, *J* = 19.2 Hz, 3H), 0.74-0.71 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.12 min, m/z (M+H)$^+$ = 462.3.

Example 3



Step 1. 6-Chloro-7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridine (3a)

[00254] To a solution of **1d** (1 g, 5.45 mmol), Cs_2CO_3 (5.32 g, 16.34 mmol) in DMF (10 mL) was added **Int. B** (27 mL, 10.87 mmol, 0.4 M in DCM). Then mixture was stirred at r.t. for 2 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with DCM (20 mL*3). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silical gel (PE/EA = 3/1) to afford compound **3a** (160 mg, 10% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.20 (s, 1H), 5.77-5.66 (m, 1H), 4.09 (s, 3H), 1.89 (d, *J* = 7.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.91 min, m/z $(M+H)^+$ = 280.1.

Step 2. 7-Methoxy-*N*-(4-methoxybenzyl)-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-amine (3b)

[00255] A mixture of **3a** (160 mg, 0.57 mmol), (4-methoxyphenyl)methanamine (157 mg, 1.14 mmo), ^{t}BuONa (110 mg, 1.14 mmol), BrettPhos (61 mg, 0.11 mmol), BrettPhos Pd G3 (52 mg, 0.057 mmol) in dioxane (2 mL) was stirred at 120 °C for 24 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and purifed by flash chromatography (DCM/MeOH = 100/1 to 30/1) to get compound **3b** (140 mg, 64% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 3.11 min, m/z $(M+H)^+$ = 381.2.

Step 3. 7-Methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-amine (3c)

[00256] A solution of **3b** (140 mg, 0.37 mmol) in TFA (2 mL) was stirred at r.t. for 16 h. The mixture was concentrated and diluted with H_2O (10 mL), basified to pH > 7 with *aq.* Na_2CO_3, extracted with EtOAc (10 mL*3), washed with brine (15 mL), dried over Na_2SO_4, concentrated

and purified by flash chromatography (DCM/MeOH = 50/1 to 5/1) to get compound **3c** (70 mg, 73% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.81 min, m/z $(M+H)^+$ = 261.1.

Step 4. 6-Chloro-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (3d)

[00257] To a solution of 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (29 mg, 0.14 mmol) and **3c** (30 mg, 0.115 mmol) in DMF (2 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 2 h and stirred at r.t. for 16 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash chromatography (MeOH in DCM is 0-6%) to get compound **3d** (25 mg, 50% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 3.15 min, m/z $(M+H)^+$ = 432.2.

Step 5. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (3)

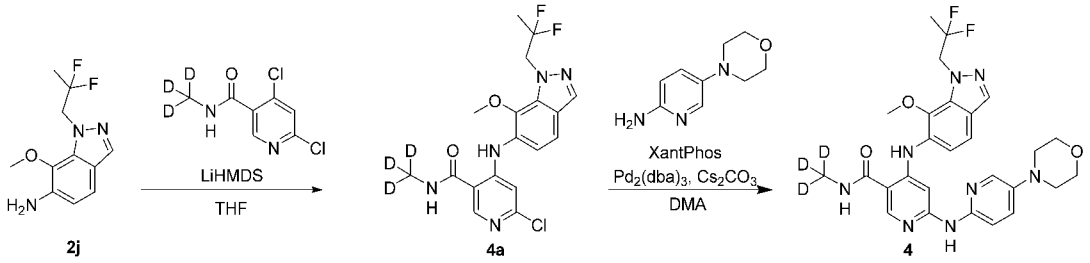
[00258] A mixture of **3d** (25 mg, 0.058 mmol), cyclopropanecarboxamide (99 mg, 1.16 mmol), BrettPhos Pd G3 (5 mg, 0.006 mmol), BrettPhos (3mg, 0.006 mmol), Cs_2CO_3 (47 mg, 0.14 mmol) in dioxane (0.5 mL) was stirred at 120 °C for 1 h under M.W. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by *prep*-HPLC (Method E) to get compound **3** (8 mg, 29% yield) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.74 (s, 1H), 9.25 (s, 1H), 8.71 (s, 1H), 8.69 (s, 1H), 8.57 (s, 1H), 8.40 (s, 1H), 5.69-5.65 (m, 1H), 3.91 (s, 3H), 2.04-2.00 (m, 1H), 1.85 (d, J = 6.8 Hz, 3H), 0.81-0.78 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.26 min, m/z $(M+H)^+$ = 481.3.

Step 6. (*R)-6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (3A) and (*S**)-6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (3B)**

[00259] **3** (8 mg, 0.017 mmol) was separated by chiral *prep*-HPLC (Method G) to afford **3A** (2.5 mg, 31% yield) as a white solid and **3B** (2.4 mg, 30% yield) as a white solid.
3A: LC-MS (ESI, Method 4) t_R = 2.25 min, m/z $(M+H)^+$ = 481.2. HPLC (Method 5) t_R = 5.92 min.

3B: LC-MS (ESI, Method 4) t_R = 2.26 min, m/z $(M+H)^+$ = 481.3. HPLC (Method 5) t_R = 7.89 min.

Example 4



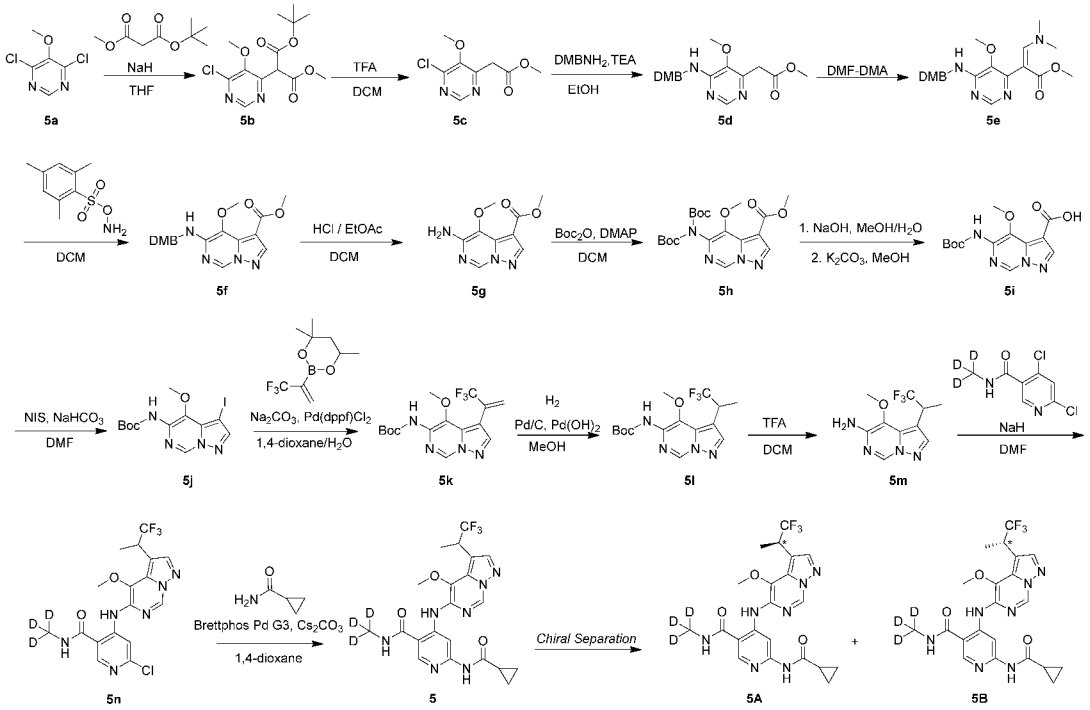
Step 1. 6-Chloro-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (4a)

[00260] To a solution of **2j** (30 mg, 0.12 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (25.9 mg, 0.12 mmol) in THF (1 mL) was added LiHMDS (0.87 mL, 0.87 mmol, 1 M in THF) at 0 °C. Then the mixture was stirred at r.t. for 2 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 30/1) to get compound **4a** (50 mg, 97% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.74 min, m/z $(M+H)^+$ = 413.2.

Step 2. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-d_3)-6-((5-morpholinopyridin-2-yl)amino)nicotinamide (4)

[00261] Compound **4a** (50 mg, 0.12 mmol), 5-morpholinopyridin-2-amine (65 mg, 0.36 mmol), XantPhos (14 mg, 0.024 mmol), Cs_2CO_3 (99 mg, 0.30 mmol) and $Pd_2(dba)_3$ (11 mg, 0.012 mmol) were dissolved in DMA (1 mL). The resulting mixture was stirred at 145 °C for 2 h. The mixture was concentrated to dryness and purified by *prep*-HPLC (Method D) to give the title compound **4** (11.4 mg, 17% yield) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 9.43 (s, 1H), 8.47 (s, 1H), 8.45 (s, 1H), 8.16 (s, 1 H), 7.77 (d, J = 3.2 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.37 (dd, J = 9.2 Hz, J = 2.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.98 (t, J = 13.2 Hz, 2H), 3.81 (s, 3H), 3.73-3.71 (m, 4H), 3.03-3.01 (m, 4H), 1.67 (t, J = 19.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.27 min, m/z $(M+H)^+$ = 556.4.

Example 5



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

[00262] To a solution of *tert*-butyl methyl malonate (53.52 g, 307 mmol) in THF (600 mL) was added NaH (22.35 g, 559 mmol, 60% purity in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 30 min. Then a solution of **5a** (50 g, 279 mmol) in THF (100 mL) was added to the mixture at 0 °C. The mixture was stirred at 80 °C for 2 h and poured into ice-water (400 mL). The mixture was acidfied with 2 *N* HCl to adjust to pH = 2 and extracted with EtOAc (500 mL*2). The organic layer was washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated to afford **5b** (88 g, 100% yield) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 1.33 min, m/z $(M+H)^+$ = 317.2.

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

[00263] A mixture of **5b** (70 g, 177 mmol) in HCl / EtOAc (2 M, 400 mL) was stirred at 30 °C overnight. The reaction mixture was concentrated. The residue was diluted with EtOAc (100 mL), adjusted to pH = 10 with *sat.* Na_2CO_3 (150 mL). The mixture was extracted with EtOAc (200 mL*3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to afford **5c** (38 g, 100% yield) as a yellow oil, which was used for the next step

directly without further purification. LC-MS (ESI, Method 3) t_R = 1.05 min, m/z $(M+H)^+$ = 217.2.

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

[00264] A mixture of **5c** (54 g, 199 mmol), TEA (40 g, 399 mmol) and $DMBNH_2$ (37 g, 219 mol) in EtOH (300 mL) was stirred at 80 °C for 5 h. After cooling to 5 °C, the formed solid was collected by filtering and dried to afford **5d** (1.33 g, 83% yield) as a white solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 1.05 min, m/z $(M+H)^+$ = 348.2.

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

[00265] A mixture of **5d** (17.5 g, 50.38 mmol) and DMF-DMA (18.05 g, 151 mmol) was stirred at 130 °C for 6 h. The mixture was concentrated to afford crude **5e** (20.27 g, yield given) as a brown oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 1.38 min, m/z $(M+H)^+$ = 403.3.

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

[00266] To a mixture of **5e** (21.5 g crude, 48.1 mmol) in DCM (200 mL) was added dropwise a solution of *O*-(mesitylsulfonyl)hydroxylamine (28.75 g, 80.14 mmol, 60% wt in H_2O) in DCM (100 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was poured into ice-*sat.*$NaHCO_3$ (70 mL) and extracted with DCM (150 mL*2). The combined orgainc layer was concentrated and the residue was purified by flash chromatography on silica gel (DCM/EtOAc = 5/1) to afford **5f** (11.25 g, 63% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.27 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* =2.4 Hz, 1H), 6.41 (dd, *J* = 8.4, 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 (5g)

[00267] To a solution of **5f** (17.7 g, 47.53 mmol) in DCM (40 mL) was added HCl / EtOAc (120 mL, 2 M). The mixture was stirred at 30 °C for 1 h. The mixture was concentrated and the residue was diluted with H_2O (100 mL). The suspension was basidied with 2 M *aq.* NaOH to pH

= 13. The solid was filtered and the filter cake was treated with DCM/MeOH (200 mL) at refluxing for 1 h. The solid was filtered off and the filtrate was concentrated to afford **5g** (8.2 g, 78% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.32 (s, 1H), 4.91 (s, 2H), 3.88 (s, 6H).

Step 7. Methyl 5-[bis(*tert*-butoxycarbonyl)amino]-4-methoxy-pyrazolo[1,5-*c*]pyrimidine-3-carboxylate (5h)

[00268] A mixture of **5g** (8.2 g, 36.94 mmol), Boc_2O (20.15 g, 92.34 mmol) and DMAP (901 mg, 7.29 mmol) in DCM (125 mL) was stirred at 30 °C for 6 h. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford **5h** (14.4 g, 92% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.50 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 1.46 (s, 18H).

Step 8. 5-((*Tert*-butoxycarbonyl)amino)-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylic acid (5i)

[00269] To a mixture of **5h** (13.5 g, 31.96 mmol) in MeOH (200 mL) and H_2O (100 mL) was added NaOH (1.92 g, 47.94 mmol) at r.t.. The mixture was stirred at 40 °C for 10 h. After cooling to r.t., the organic layer was removed under reduced pressure and the aqueous layer was acidified by 2 *N aq.* HCl to pH = 1. The formed solid was filtered and dried to afford a white solid. The obtained white solid, K_2CO_3 (12.17 g, 88.03 mmol) and MeOH (80 mL) was stirred at 70 °C for 3 h. Then, the mixture was concentrated and the residue was acidified by 2 *N aq.* HCl to pH = 1. The formed solid was filtered and dried to afford **5i** (7.42 g, 71% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.52 (s, 1H), 7.33 (s, 1H), 3.97 (s, 3H), 1.57 (s, 9H).

Step 9. *Tert*-butyl (3-iodo-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)carbamate (5j)

[00270] To a mixture of **5i** (3.3 g, 10.70 mmol) and NIS (4.82 g, 21.41 mmol) in DMF (45 mL) was added $NaHCO_3$ (2.70 g, 32.11 mmol) at 0 °C. After stirring at 10 °C for 2 h, the reaction mixture was diluted with *aq.* $Na_2S_2O_3$ (350 mL) and extracted with EtOAc (100 mL*3). The organic layer was washed with brine (100 mL*3), dried over Na_2SO_4, filtered and the filtrate was concentrated to afford **5j** (2.97 g, 71% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 9.19 (s, 1H), 8.21 (s, 1H), 3.83 (s, 3H), 1.49 (s, 9H).

Step 10. *Tert*-butyl (4-methoxy-3-(3,3,3-trifluoroprop-1-en-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)carbamate (5k)

[00271] A mixture of **5j** (145 mg, 0.37 mmol), 4,4,6-trimethyl-2-[1-(trifluoromethyl)vinyl]-1,3,2-dioxaborinane (165 mg, 0.74 mmol), Na_2CO_3 (79 mg, 0.74 mmol) and $Pd(dppf)Cl_2$ (27 mg, 0.04 mmol) in 1,4-dioxane/H_2O (0.5 mL/0.1 mL) was stirred at 70 °C for 6 h and 90 °C for 3 h. After cooling to r.t., the reaction mixture was diluted with EtOAc (10 mL), washed with water (5 mL) and brine (5 mL). The organic layer dried over Na_2SO_4, filtered and the filtrate was concentrated to afford **5k** (130 mg, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 1.28 min, m/z $(M-^tBu+H)^+$ = 303.1.

Step 11. *Tert*-butyl (4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)carbamate (5l)

[00272] A mixture of **5k** (130 mg, 0.36 mmol), Pd/C (150 mg, 50% wt. wetted in water) and $Pd(OH)_2$ (150 mg, Pd 20% on carbon, wetted in water 50% water) in MeOH (2 mL) was stirred at 50 °C for 3 days under H_2 (50 Psi) atmosphere. The mixture was filtered and the filtrate was concentrated to afford **5l** (130 mg, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 1.35 min, m/z $(M-^tBu+H)^+$ = 305.0.

Step 12. 4-Methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-amine (5m)

[00273] A mixture of **5l** (125 mg, 0.35 mmol) and TFA/DCM (2 mL/6 mL) was stirred at 0 °C for 1 h. The solvent was removed by pumping nitrogen stream. The residue was diluted with DCM (3 mL), adjusted to pH>7 with NH_3/1,4-dioxane (2 M). The mixture was concentrated and the residue was purified by flash chromatography on silical gel (DCM/EtOAc = 10/1) to afford **5m** (59 mg, 65% yield) as a yellow oil. LC-MS (ESI, Method 3) t_R = 1.17 min, m/z $(M+H)^+$ = 261.0.

Step 13. 6-Chloro-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (5n)

[00274] To a solution of **5m** (50 mg, 0.19 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (120 mg, 0.58 mmol) in DMF (1 mL) was added NaH (23 mg, 0.58 mmol, 60% in mineral oil) at

0 °C. Then the mixture was stirred at 15 °C for 3 h. The reaction mixture was quenched with ice-water (3 mL) and extracted with EtOAc (5 mL*3). The organic layer was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **5n** (10 mg, 12% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 1.26 min, m/z $(M+H)^+$ = 432.3.

Step 14. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (5)

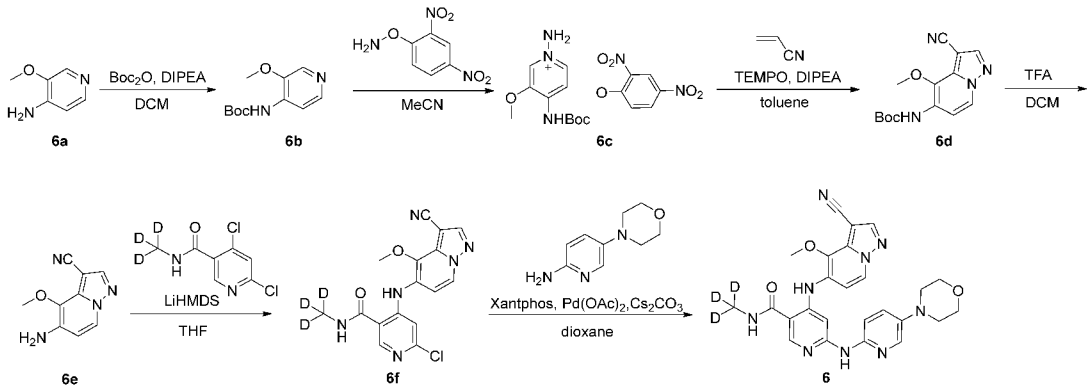
[00275] A mixture of **5n** (10.0 mg, 0.023 mmol), cyclopropanecarboxamide (10.0 mg, 0.12 mmol), Cs_2CO_3 (15 mg, 0.046 mmol) and Brettphos Pd G3 (4 mg, 0.005 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C for 10 h under N_2 atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **5** (3 mg, 27% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 10.76 (s, 1H), 9.33 (s, 1H), 8.86 (s, 1H), 8.69 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 4.11-4.05 (m, 1H), 3.87 (s, 3H), 2.02-1.96 (m, 1H), 1.55 (d, J = 7.2 Hz, 3H), 0.81-0.79 (m, 4H). LC-MS (ESI, Method 2) t_R = 3.25 min, m/z $(M+H)^+$ = 481.1.

Step 15. (*R)-6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (5A) and (*S**)-6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (5B)**

[00276] Compound **5** (10 mg, 0.021 mmol) was separated by chiral *prep*-HPLC (Method H) to afford **5A** (3 mg, 27% yield) as a white solid and **5B** (3 mg, 27% yield) as a white solid. **5A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 10.76 (s, 1H), 9.33 (s, 1H), 8.85 (s, 1H), 8.70 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 4.11-4.07 (m, 1H), 3.87 (s, 3H), 2.02-1.97 (m, 1H), 1.55 (d, J = 7.2 Hz, 3H), 0.81-0.79 (m, 4H). LC-MS (ESI, Method 2) t_R = 3.23 min, m/z $(M+H)^+$ = 481.0. HPLC (Method 6) t_R = 5.00 min.

[00277] **5B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 10.76 (s, 1H), 9.33 (s, 1H), 8.85 (s, 1H), 8.69 (s, 1H), 8.58 (s, 1H), 8.26 (s, 1H), 4.11-4.07 (m, 1H), 3.87 (s, 3H), 2.02-1.97 (m, 1H), 1.55 (d, J = 7.2 Hz, 3H), 0.81-0.79 (m, 4H). LC-MS (ESI, Method 2) t_R = 3.24 min, m/z $(M+H)^+$ = 481.0. HPLC (Method 6) t_R = 7.03 min.

Example 6



Step 1. *Tert*-butyl (3-methoxypyridin-4-yl)carbamate (6b)

[00278] A solution of **6a** (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 (EtOAc in PE is 10-50%) to give **6b** (1.45 g, yield given) as a white solid. LC-MS (ESI, Method 4) t_R = 1.92 min, m/z $(M+H)^+$ = 225.1.

Step 2. 1-Amino-4-((*tert*-butoxycarbonyl)amino)-3-methoxypyridin-1-ium 2,4-dinitrophenolate (6c)

[00279] A mixture of **6b** (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 **6c** (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. *Tert*-butyl (3-cyano-4-methoxypyrazolo[1,5-*a*] pyridin-5-yl) carbamate (6d)

[00280] A mixture of **6c** (88 mg, 0.208 mmol), acrylonitrile (27 mg, 0.312 mmol), TEMPO (40 mg, 0.25 mmol) and DIPEA (54 mg, 0.416 mmol, 73 μL) in toluene (1 mL) was stirred at 40 °C for 12 h. A black solution was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*2). The combined organic layer was washed with brine (40 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatograph (EtOAc in PE is 10-50%) to give **6d** (30 mg, 50% yield over 2 steps) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.22 (brs, 1H), 4.04 (s, 3H), 1.56 (s, 9H). LC-MS (ESI, Method 4) t_R = 4.02 min,

m/z $(M+H)^+$ = 289.1.

Step 4. 5-Amino-4-methoxypyrazolo[1,5-*a*]pyridine-3-carbonitrile (6e)

[00281] To a mixture of **6d** (30 mg, 0.104 mmol) in DCM (3 mL) was added TFA (1.49 g, 13.1 mmol, 1 mL) at 0 °C. The resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated and diluted with H_2O (10 mL), adjusted pH > 7 with aq Na_2CO_3, extracted with EtOAc (10 mL*3) washed with brine, dried in vacuo to give **6e** (18 mg, 92% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 1.97 min, m/z $(M+H)^+$ = 189.0.

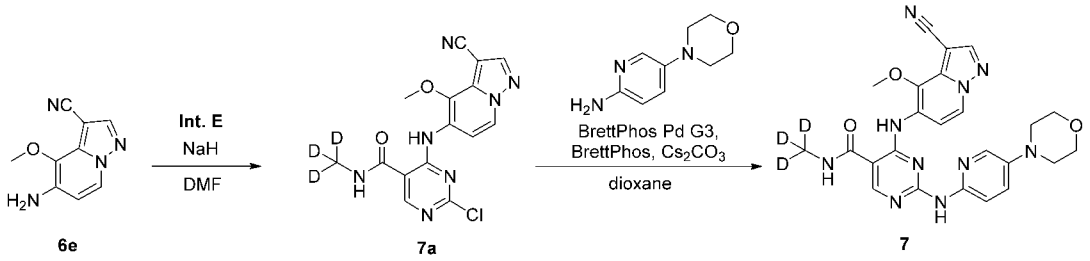
Step 5. 6-Chloro-4-((3-cyano-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-(methyl-*d*$_3$)nicotinamide (6f)

[00282] To a solution of **6e** (18 mg, 0.096 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (20 mg, 0.096 mmol) in THF (0.5 mL) was added LiHMDS (0.67 mL, 0.67 mmol, 1 M in THF) at 0 °C. The resulting mixture was stirred at 10 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3) washed with brine (10 mL), dried in vacuo to give **6f** (30 mg, 88% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.41 min, m/z $(M+H)^+$ = 360.1.

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

[00283] To a solution **6f** (30 mg, 0.083 mmol) and 5-morpholinopyridin-2-amine (30 mg, 0.17 mmol) in dioxane (0.5 mL) was added XantPhos (10 mg, 0.017 mmol) and Cs_2CO_3 (54 mg, 0.17 mmol) and $Pd(OAc)_2$ (2 mg, 0.008 mmol) at 25 °C, the reaction mixture was stirred at 100 °C for 12 hours under N_2 atmosphere, the mixture was diluted with H_2O (2 mL), extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na_2SO_4, concentrated and purified by *prep*-HPLC (Method E) to get the compound **6** (6.5 mg, 16% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 9.71 (s, 1H), 8.55 (s, 1H), 8.49 (s, 1H), 8.14 (s, 1H), 7.95-7.93 (m, 2H), 7.75 (d, *J* = 6.4 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.41 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 6.95 (d, *J* = 6.4 Hz, 1H), 3.74 (t, *J* = 4.8 Hz, 4H), 3.66 (s, 3H), 3.03 (t, *J* = 4.8 Hz, 4H). LC-MS (ESI, Method 4) t_R = 1.72 min, m/z $(M+H)^+$ = 503.3.

Example 7



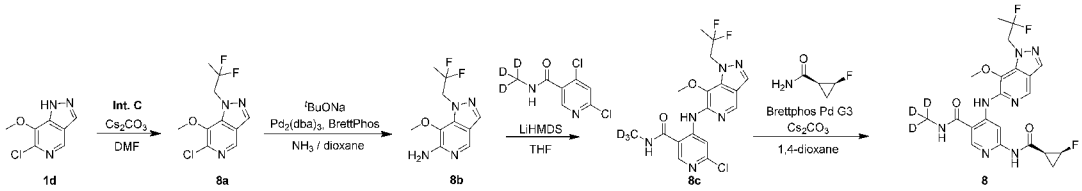
Step 1. 2-Chloro-4-((3-cyano-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-(methyl-d_3)pyrimidine-5-carboxamide (7a)

[00284] To a mixture of **Int. E** (45 mg, 0.212 mmol) and **6e** (40 mg, 0.212 mmol) in DMF (3 mL) was added NaH (60 mg, 1.49 mmol, 60% in mineral oil) at 0 °C. The resulting mixture was stirred at 0-20 °C for 2 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude product. The crude product was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **7a** (30 mg, 39% yield) as a yellow solid. LC-MS (ESI, Method 4), t_R = 2.53 min, m/z $(M+H)^+$ = 361.2.

Step 2 4-((3-Cyano-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-(methyl-d_3)-2-((5-morpholinopyridin-2-yl)amino)pyrimidine-5-carboxamide (7)

[00285] A mixture of **7a** (30 mg, 0.083 mmol), 5-morpholinopyridin-2-amine (18 mg, 0.10 mmol), BrettPhos (10 mg, 0.017 mmol), Cs_2CO_3 (81 mg, 0.25 mmol) and BrettPhos Pd G3 (8 mg, 0.008 mmol) in dioxane (1 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 concentrated and purified by *prep*-HPLC (Method E) to give compound **7** (1.6 mg, 3.8% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 10.14 (s, 1H), 9.03 (d, J = 6.8 Hz, 1H), 8.76 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.62 (s, 1H), 8.56 (s, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.84 (d, J = 6.8 Hz, 1H), 7.46 (dd, J = 9.2, 3.2 Hz, 1H), 3.98 (s, 3H), 3.77 (t, J = 4.8 Hz, 4H), 3.15 (t, J = 4.8 Hz, 4H). LC-MS (ESI, Method 4) t_R = 2.43 min, m/z $(M+H)^+$ = 504.3.

Example 8



Step 1. 6-Chloro-1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridine (8a)

[00286] A mixture of **1d** (400 mg, 2.18 mmol), **Int. C** (1.6 g, 7.01 mmol), Cs_2CO_3 (1.42 g, 4.36 mmol) in DMF (5 mL) was stirred at 30 °C for 1 h. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (15 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silical gel (PE/EA = 3/1) to afford **8a** (120 mg, 21% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.45 (s, 1H), 4.98 (t, J = 13.6 Hz, 2H), 4.02 (s, 3H), 1.71 (t, J = 19.2 Hz, 3H).

Step 2. 1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-amine (8b)

[00287] A mixture of **8a** (266 mg, 1 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol), BrettPhos (27 mg, 0.050 mmol) and ^{t}BuONa (147 mg, 1.52 mmol) in *sat.* NH_3/dioxane (4 mL) was stirred at 100 °C for 12 h under N_2. The mixture was cooled and concentrated. The residue was purified by *prep*-HPLC (Method A) to afford **8b** (100 mg, 41% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 1.27 min, m/z $(M+H)^+$ = 243.2.

Step 3. 6-Chloro-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (8c)

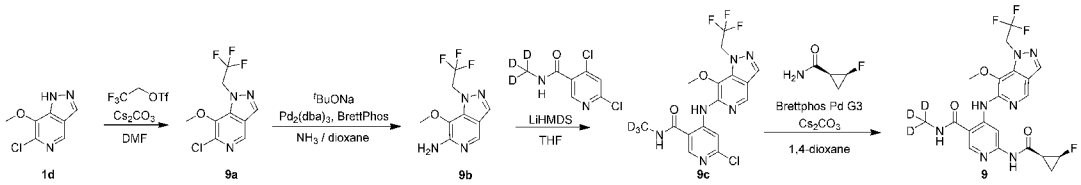
[00288] To a solution of **8b** (90 mg, 0.37 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (93 mg, 0.45 mmol) in THF (0.8 mL) was added LiHMDS (1.5 mL, 1.5 mmol, 1 M in THF) at -40 °C. The reaction was stirred at -40 °C to r.t. for 1 h and quenched with H_2O (1 mL). The organic solvent was evaporated under reduce pressure. The formed solid was collected by filtering and was dried to afford **8c** (50 mg, 38% yield) as a red solid. LC-MS (ESI, Method 3) t_R = 1.60 min, m/z $(M+H)^+$ = 414.2.

Step 4. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-*N*-(methyl-d_3)nicotinamide (8)

[00289] A mixture of **8c** (32 mg, 0.08 mmol), (1*S*, 2*S*)-2-fluorocyclopropane-1-carboxamide

(40 mg, 0.40 mmol), BrettPhos Pd G3 (14 mg, 0.015 mmol) and Cs_2CO_3 (50 mg, 0.15 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C overnight under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford compound **8** (5.8 mg, 16% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.76 (s, 1H), 9.23 (s, 1H), 8.71 (s, 1H), 8.68 (s, 1H), 8.58 (s, 1H), 8.33 (s, 1H), 5.00-4.82 (m, 3H), 3.90 (s, 3H), 2.23-2.20 (m, 1H), 1.69 (t, J = 19.2 Hz, 3H), 1.65-1.60 (m, 1H), 1.18-1.23 (m, 1H). LC-MS (ESI, Method 2) t_R = 3.46 min, m/z $(M+H)^+$ = 481.2.

Example 9



Step 1. 6-Chloro-7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazolo[4,3-*c*]pyridine (9a)

[00290] A mixture of **1d** (1 g, 5.4 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.5 g, 11 mmol) and Cs_2CO_3 (3.5 g, 11 mmol) in DMF (10 mL) was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silical gel (PE/EA = 3/1) to afford compound **9a** (254 mg, 18% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.23 min, m/z $(M+H)^+$ = 266.0.

Step 2. 7-Methoxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-amine (9b)

[00291] A mixture of **9a** (254 mg, 0.96 mmol), $Pd_2(dba)_3$ (17 mg, 0.019 mmol), BrettPhos (25 mg, 0.047 mmol), ^{t}BuONa (137 mg, 1.4 mmol) and *sat.* NH_3/dioxane (4 mL) was stirred at 100 °C for 12 h. The mixture was cooled, concentrated and the residue was purified by *prep*-HPLC (Method A) to afford compound **9b** (59 mg, 25% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 1.34 min, m/z $(M+H)^+$ = 247.2.

Step 3. 6-Chloro-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (9c)

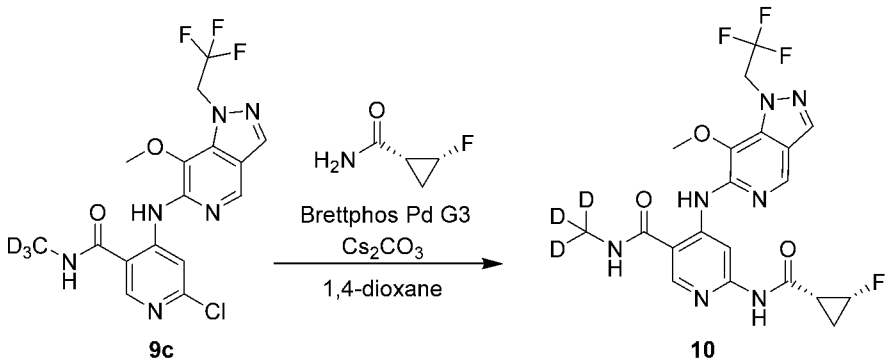
[00292] To a solution of **9b** (45 mg, 0.18 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide

(46 mg, 0.22 mmol) in THF (0.5 mL) was added LiHMDS (0.7 mL, 0.7 mmol, 1 M in THF) at -40 °C. The reaction was stirred at -40 °C to r.t. for 1 h and quenched with H_2O (2 mL). The organic solvent was evaporated under reduced pressure. The formed solid was collected by filtering and was dried to afford compound **9c** (12 mg, 16% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 1.63 min, m/z $(M+H)^+$ = 418.2.

Step 4. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (9)

[00293] A mixture of **9c** (50 mg, 0.12 mmol), (1*S*, 2*S*)-2-fluorocyclopropane-1-carboxamide (62 mg, 0.60 mmol), BrettPhos Pd G3 (22 mg, 0.024 mmol) and Cs_2CO_3 (78 mg, 0.24 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C overnight under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford compound **9** (3.3 mg, 6% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 10.78 (s, 1H), 9.27 (s, 1H), 8.73 (s, 1H), 8.70 (s, 1H), 8.59 (s, 1H), 8.39 (s, 1H), 5.34 (q, *J* = 8.0 Hz, 2H), 5.01-4.83 (m, 1H), 3.93 (s, 3H), 2.22-2.18 (m, 1H), 1.68-1.61 (m, 1H), 1.24-1.14 (m, 1H). LC-MS (ESI, Method 2) t_R = 3.33 min, m/z $(M+H)^+$ = 485.2.

Example 10



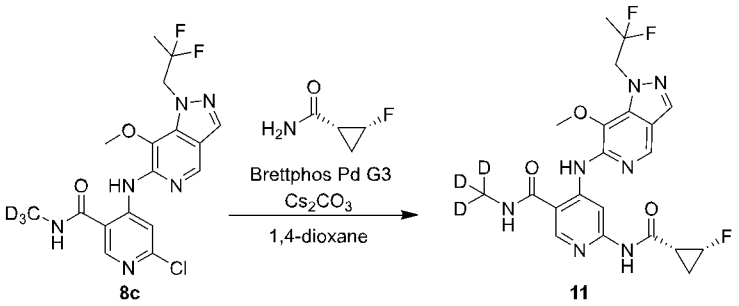
9c 10

Step 1. 6-((1*R*,2*R*)-2-fluorocyclopropane-1-carboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (10)

[00294] A mixture of **9c** (30 mg, 0.07 mmol), (1*R*, 2*R*)-2-fluorocyclopropane-1-carboxamide (37 mg, 0.36 mmol), BrettPhos Pd G3 (13 mg, 0.014 mmol) and Cs_2CO_3 (47 mg, 0.14 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C overnight under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford

10 (10 mg, 29% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 10.78 (s, 1H), 9.27 (s, 1H), 8.74 (s, 1H), 8.70 (s, 1H), 8.60 (s, 1H), 8.39 (s, 1H), 5.34 (d, J = 8.4 Hz, 2H), 5.01-4.83 (m, 1H), 3.93 (s, 3H), 2.24-2.19 (m, 1H), 1.68-1.61 (m, 1H), 1.17-1.14 (m, 1H). LC-MS (ESI, Method 2) t_R = 3.32 min, m/z $(M+H)^+$ = 485.2.

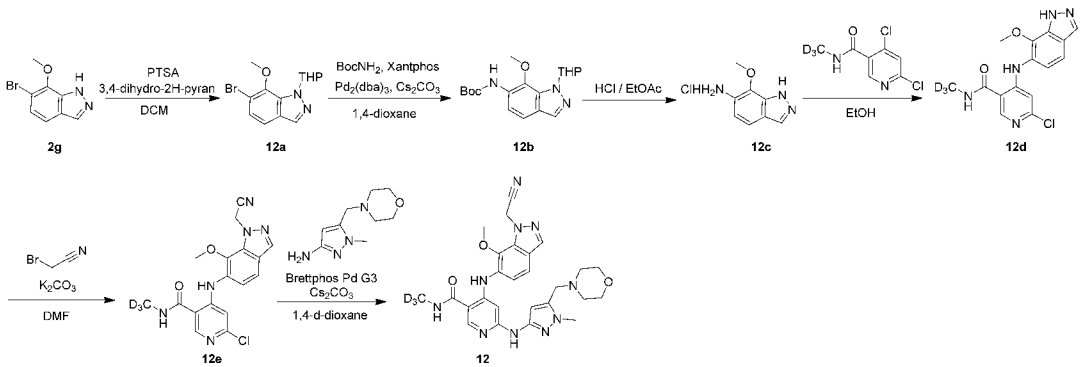
Example 11



Step 1. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-6-((1*R*,2*R*)-2-fluorocyclopropane-1-carboxamido)-*N*-(methyl-d_3)nicotinamide (11)

[00295] A mixture of **8c** (50 mg, 0.12 mmol), (1*R*, 2*R*)-2-fluorocyclopropane-1-carboxamide (62 mg, 0.60 mmol), BrettPhos Pd G3 (22 mg, 0.024 mmol) and Cs_2CO_3 (78 mg, 0.24 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C for 2 h under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford **11** (13 mg, 22% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.75 (s, 1H), 9.23 (s, 1H), 8.71 (s, 1H), 8.67 (s, 1H), 8.58 (s, 1H), 8.33 (s, 1H), 5.01-4.80 (m, 3H), 3.90 (s, 3H), 2.22-2.17 (m, 1H), 1.69 (t, J = 19.2 Hz, 3H), 1.60-1.58 (m, 1H), 1.17-1.12 (m, 1H). LC-MS (ESI, Method 2) t_R = 2.56 min, m/z $(M+H)^+$ = 481.2.

Example 12



Step 1. 6-Bromo-7-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (12a)

[00296] To a solution of **2g** (450 mg, 1.98 mmol) and 3,4-dihydro-2*H*-pyran (500 mg, 5.95 mmol, 0.54 mL) in DCM (5 mL) was added $TsOH.H_2O$ (38 mg, 0.2 mmol). After stirring at 5 °C for 12 h, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 6/1) to afford **12a** (450 mg, 73% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.41 min, m/z (^{79}Br, $M+H)^+$ = 311.1.

Step 2. *Tert*-butyl (7-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-6-yl)carbamate (12b)

[00297] A mixture of **12a** (400 mg, 1.29 mmol), Cs_2CO_3 (838 mg, 2.57 mmol), $Pd_2(dba)_3$ (118 mg, 0.13 mmol), $BocNH_2$ (301 mg, 2.57 mmol) and Xantphos (74 mg, 0.13 mmol) in 1,4-dioxane (3 mL) was stirred at 100 °C under N_2 for 12 h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to afford **12b** (400 mg, 90% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.39 min, m/z $(M-84+H)^+$ = 264.2.

Step 3. 7-Methoxy-1*H*-indazol-6-amine hydrochloride (12c)

[00298] A solution of **12b** (400 mg, 1.15 mmol) in HCl / EtOAc (4 mL, 2M) was stirred at 35 °C for 2 h. The formed solid was collected by filtering and was dried to afford **12c** (200 mg, 87% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 0.36 min, m/z $(M+H)^+$ = 163.9.

Step 4. 6-Chloro-4-((7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (12d)

[00299] To a solution of **12c** (200 mg, 1.00 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (271 mg, 1.30 mmol) in EtOH (2 mL) was stirred at 80 °C for 12 h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford **12d** (200 mg, 60% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.06 min, m/z $(M+H)^+$ = 335.0.

Step 5. 6-Chloro-4-((1-(cyanomethyl)-7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (12e)

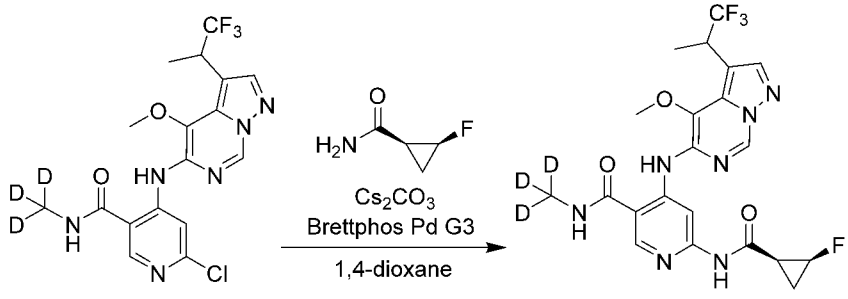
[00300] To a solution of **12d** (130 mg, 0.39 mmol) in DMF (1.5 mL) was slowly added NaH (47 mg, 1.16 mmol, 60% in mineral oil) at 0 °C and stirred at 0 °C for 30 min. Then 2-bromoacetonitrile (70 mg, 0.58 mmol, 0.04 mL) was added to the mixture at 0 °C. After stirring

at 25 °C for 12 h, the reaction solution was poured into ice-water (5 mL) and extracted with EtOAc (10 mL*2). The combined organic phase was washed with brine (5 mL), dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 30/1) to afford **12e** (85 mg, 59% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.15 min, m/z $(M+H)^+$ = 374.2.

Step 6. 4-((1-(Cyanomethyl)-7-methoxy-1*H*-indazol-6-yl)amino)-*N*-(methyl-d_3)-6-((1-methyl-5-(morpholinomethyl)-1*H*-pyrazol-3-yl)amino)nicotinamide (12)

[00301] A mixture of **12e** (50 mg, 0.13 mmol), 1-methyl-5-(morpholinomethyl)pyrazol-3-amine (32 mg, 0.16 mmol, CAS: 1328640-42-1), Cs_2CO_3 (87 mg, 0.27 mmol) and BrettPhos Pd G3 (24 mg, 0.027 mmol) in 1,4-dioxane (0.5 mL) was stirred at 110 °C under N_2 atmosphere for 12 h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to afford **12** (17.5 mg, 25% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 9.20 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.25 (s, 1H), 6.04 (s, 1H), 5.75 (s, 2H), 3.87 (s, 3H), 3.61 (s, 3H), 3.55-3.53 (m, 4H), 3.42 (s, 2H), 2.34-2.32 (m, 4H). LC-MS (ESI, Method 2) t_R = 1.99 min, m/z $(M+H)^+$ = 534.3.

Example 13

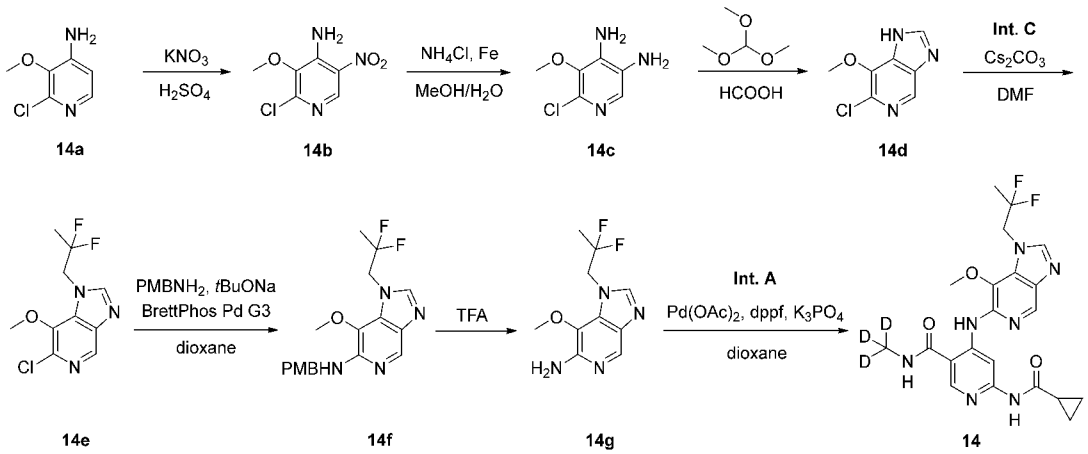


Step 1. 6-((1*S*,2*S*)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (13)

[00302] A mixture of **5n** (10 mg, 0.023 mmol), (1*S*,2*S*)-2-fluorocyclopropane-1-carboxamide (12 mg, 0.12 mmol), BrettPhos Pd G3 (4 mg, 0.005 mmol) and Cs_2CO_3 (15 mg, 0.05 mmol) in 1,4-dioxane (0.5 mL) was stirred at 90 °C overnight under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by *prep*-HPLC (Method A) to afford

13 (0.6 mg, 5% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 10.83 (s, 1H), 9.37 (s, 1H), 8.89 (s, 1H), 8.73 (s, 1H), 8.61 (s, 1H), 8.28 (s, 1H), 5.01-4.83 (m, 1H), 4.13-4.11 (m, 1H), 3.90 (s, 3H), 2.21-2.18 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H), 1.18-1.16 (m, 1H), 1.09-1.05 (m, 1H). LC-MS (ESI, Method 2) t_R = 3.24 min, m/z $(M+H)^+$ = 499.0.

Example 14



Step 1. 2-Chloro-3-methoxy-5-nitropyridin-4-amine (14b)

[00303] To a solution of **14a** (1.0 g, 6.31 mmol) in *conc.* H_2SO_4 (10 mL) was added KNO_3 (701 mg, 6.94 mmol) at 0 °C, then the mixture was stirred at r.t. for 4 h. The mixture was poured into ice-water, basified to pH = 13 with $NH_3.H_2O$, extracted with EtOAc (50 mL*5), washed with brine (50 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (PE/EA = 10/1 to 1/1) to get compound **14b** (800 mg, 62% yield) as a pale yellow solid. LC-MS (ESI, Method 4) t_R = 1.88 min, m/z $(M+H)^+$ = 204.1.

Step 2. 6-Chloro-5-methoxypyridine-3,4-diamine (14c)

[00304] To a solution of **14b** (350 mg, 1.72 mmol) in MeOH (4 mL) and H_2O (1 mL) was added Fe powder (480 mg, 8.60 mmol) and NH_4Cl (460 mg, 8.6 mmol). Then the mixture was stirred at 70 °C for 2 h. The mixture was filtered and washed with EtOAc (10 mL). Then the filtrate was concentrated and diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na_2SO_4, concentrated and purified by flash chromatography (DCM/MeOH = 50/1 to 5/1) to get compound **14c** (290 mg, 97% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 0.46 min, m/z $(M+H)^+$ = 174.1.

Step 3. 6-Chloro-7-methoxy-1*H*-imidazo[4,5-*c*]pyridine (14d)

[00305] To a solution of **14c** (290 mg, 1.67 mmol) in trimethoxymethane (1.77 g, 16.71 mmol, 1.83 mL) was added formic acid (80 mg, 1.67 mmol), then the mixture was stirred at 100 °C for 1 h. The mixture was concentrated and diluted with H_2O (20 mL), extracted with EtOAc (15 mL*3), washed with brine (15 mL), dried over Na_2SO_4, concentrated to get compound **14d** (300 mg, 98% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.88 min, m/z $(M+H)^+$ = 184.1.

Step 4. 6-Chloro-1-(2,2-difluoropropyl)-7-methoxy-1*H*-imidazo[4,5-*c*]pyridine (14e)

[00306] To a solution of **14d** (300 mg, 1.63 mmol) in DMF (5 mL) was added Cs_2CO_3 (1.60 g, 4.90 mmol) and **Int. C** (559 mg, 2.45 mmol). Then the mixture was stirred at r.t. for 4 h. Then the mixture was diluted with H_2O (30 mL), extracted with EA (20 mL*3), washed with brine (20 mL), dired over Na_2SO_4, concentrated and purified by *prep*-TLC (DCM/MeOH = 30/1) to get compound **14e** (120 mg, 28% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.94 (s, 1H), 4.74 (t, *J* = 13.2 Hz, 2H), 4.07 (s, 3H), 1.71 (t, *J* = 18.4 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.16 min, m/z $(M+H)^+$ = 262.1.

Step 5. 1-(2,2-Difluoropropyl)-7-methoxy-*N*-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridin-6-amine (14f)

[00307] A mixture of **14e** (120 mg, 0.46 mmol), (4-methoxyphenyl)methanamine (126 mg, 0.92 mmol), BrettPhos Pd G3 (83 mg, 0.091 mmol), *t*BuONa (88 mg, 0.92 mmol) in THF (1.5 mL) was stirred at 90 °C for 2 h. The mixture was concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 20/1) to get compound **14f** (150 mg, 90% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 1.98 min, m/z $(M+H)^+$ = 363.2.

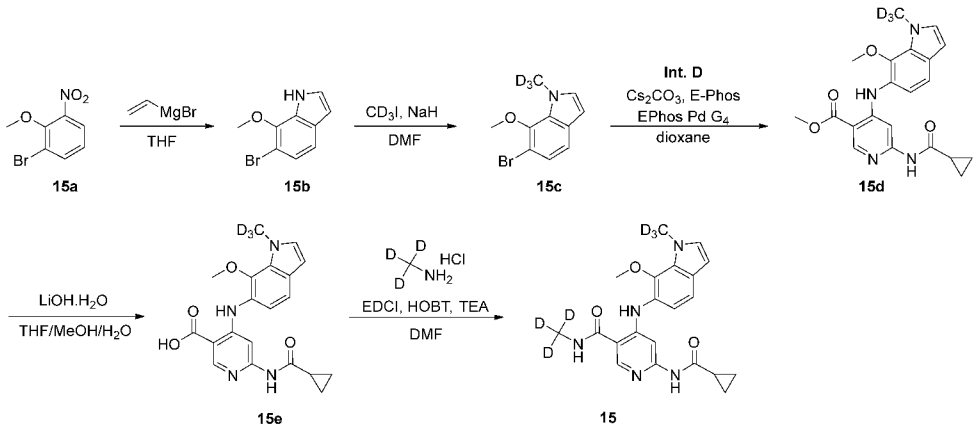
Step 6. 1-(2,2-Difluoropropyl)-7-methoxy-1*H*-imidazo[4,5-*c*]pyridin-6-amine (14g)

[00308] A solution of **14f** (150 mg, 0.41 mmol) in TFA (2 mL) was stirred at r.t. for 2 h. The mixture was concentrated and diluted with H_2O (20 mL), adjusted to pH > 7 with *aq.* Na_2CO_3 and extracted with EtOAc (20 mL*3). The combined organic layer was washed with brine (30 mL*2), dried over Na_2SO_4, concentrated and purified by flash chromagraphy (DCM/MeOH = 100/1 to 5/1) to get compound **14g** (90 mg, 90% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.50 min, m/z $(M+H)^+$ = 243.1.

Step 7. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-imidazo[4,5-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (14)

[00309] A mixture of **14g** (2 mg, 0.008 mmol), **Int. A** (2 mg, 0.008 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), dppf (4 mg, 0.008 mmol), K_3PO_4 (4 mg, 17 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 16 h. The mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **14** (1.0 mg, 26% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 10.65 (s, 1H), 9.09 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 4.82 (t, J = 14.4 Hz, 2H), 3.84 (s, 3H), 1.97-1.95 (m, 1H), 1.71 (t, J = 19.2 Hz, 3H), 0.77-0.73 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.01 min, m/z $(M+H)^+$ = 463.3.

Example 15



Step 1. 6-Bromo-7-methoxy-1*H*-indole (15b)

[00310] To a solution of **15a** (17 g, 219.9 mmol) in THF (100 mL) at -40 °C under N_2 atmosphere was added vinylmagnesium bromide (220 mL, 220 mmol, 1 M in THF). The resulting mixture was stirred at -20 °C for 30 min. The reaction was then quenched with *aq.* NH_4Cl (300 mL) and extracted with EA (300 mL*3). The combined organic layer was washed by brine (300 mL*2), dried over sodium sulphate and evaporated in vacuo. The residue was purified by flash chromatography (EA in PE is 5-10%) to give **15b** (4.78 g, 20% yield) as a yellow oil. LC-MS (ESI, Method 2), t_R = 1.88 min, m/z (^{79}Br, $M+H)^+$ = 225.9.

Step 2. 6-Bromo-7-methoxy-1-(methyl-d_3)-1*H*-indole (15c)

[00311] To a solution of **15b** (4.5 g, 19.9 mmol) in DMF (50 mL) at 0 °C under N_2 atmosphere was added NaH (1.19 g, 29.85 mmol, 60% in mineral oil). The resulting mixture was

stirred at 0 °C for 30 min and added iodomethane-d_3 (3.17 g, 21.89 mmol). The resulting mixture was stirred at 25 °C for 16 h. The reaction was then quenched with *aq.* NH_4Cl (50 mL) and extracted with EA (200 mL*3). The combined organic layer was washed by brine (200 mL*2), dried over sodium sulphate and evaporated in vacuo. The residue was purified by flash chromatography (EA in PE is 5-15%) to give **15c** (4.57 g, 68% yield) as a yellow oil. LC-MS (ESI, Method 2), t_R = 2.19 min, m/z (^{79}Br, M+H)$^+$ = 243.0.

Step 3. Methyl 6-(cyclopropanecarboxamido)-4-((7-methoxy-1-(methyl-d_3)-1*H*-indol-6-yl)amino)nicotinate (15d)

[00312] To a solution of **15c** (400 mg, 1.64 mmol) in dioxane (6 mL) was added **Int. D** (402 mg, 1.15 mmol), Cs_2CO_3 (1.61 g, 4.94 mmol), EPhos (87.9 mg, 0.164 mmol) and EPhos Pd G_4 (221.4 mg, 0.25 mmol). The reaction mixture was stirred at 90 °C under N_2 atmosphere for 16 h. The mixture was cooled to room temperature and diluted with water (30 mL), extracted with EA (30 mL*3). The combined organic layer was washed by brine (50 mL*2), dried over sodium sulphate, evaporated in vacuo and purified by *prep*-TLC (DCM/MeOH = 20/1) to give **15d** (120 mg, 11% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.76 min, m/z (M+H)$^+$ = 398.2.

Step 4. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(methyl-d_3)-1*H* -indol-6-yl)amino)nicotinic acid (15e)

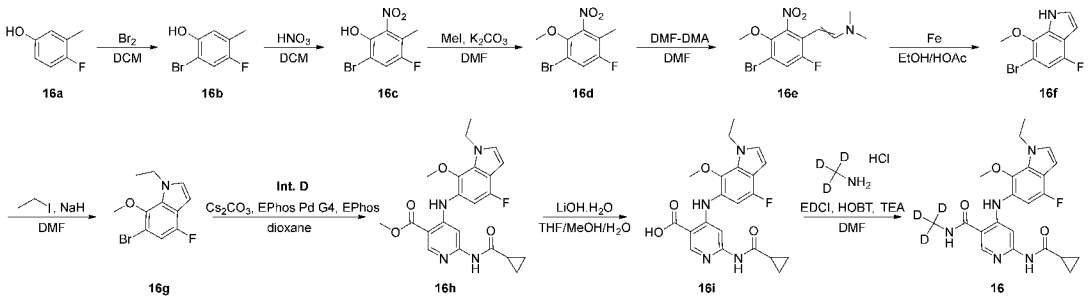
[00313] To a solution of **15d** (110 mg, 0.28 mmol) in THF/MeOH/H_2O = 3/2/1 (6 mL) was added LiOH.H_2O (23.2 mg, 0.55 mmol) and stirred at 40 °C under N_2 atmosphere for 16 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL*3). The combined organic layer was washed by brine (20 mL*2), dried over sodium sulphate, evaporated in vacuo and purified by *prep*-TLC (DCM/MeOH = 10/1) to give **15e** (85 mg, 69% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.49 min, m/z (M+H)$^+$ = 384.0.

Step 5. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(methyl-d_3)-1*H* -indol-6-yl)amino)-*N*-(methyl- d_3)nicotinamide (15)

[00314] To a solution of **15e** (85 mg, 0.22 mmol) in DMF (2 mL) was added CD_3NH_2.HCl (23.5 mg, 0.33 mmol), EDCI (51.1 mg, 0.266 mmol), HOBt (36 mg, 0.266 mmol) and TEA (112 mg, 1.11 mmol, 0.15 mL). The reaction mixture was stirred at 25 °C under N_2 atmosphere for 16 h. The mixture was diluted with water (20 mL) and extracted with EA (10 mL*3). The combined

organic layer was washed by brine (10 mL*2), dried over sodium sulphate, evaporated in vacuo and purified by *prep*-TLC (DCM/MeOH = 10/1) to give **15** as a crude (26 mg). Then the crude product was purified by *prep*-HPLC (Method F) to give **15** (5.6 mg, 6% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 10.34 (s, 1H), 8.52-8.48 (m, 2H), 7.71 (s, 1H), 7.27-7.25 (m, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 3.73 (s, 3H), 1.94-1.92 (m, 1H), 0.72-0.69 (m, 4H). LC-MS (ESI, Method 4), t_R = 2.49 min, m/z $(M+H)^+$ = 400.1.

Example 16



Step 1. 2-Bromo-4-fluoro-5-methylphenol (16b)

[00315] To a solution of **16a** (10 g, 79.3 mmol) in DCM (140 mL) was added Br_2 (15.21 g, 95.1 mmol, 4.89 mL) under nitrogen at 25 °C. The reaction mixture was stirred at 25 °C for 16 h. The reaction was quenched by water (100 mL) and extracted with EA (100 mL*2), washed with water (100 mL*2) and brine (100 mL*2), dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography (PE) to give **16b** (14 g, 73% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 6.8 Hz, 1H), 2.20 (s, 3H).

Step 2. 6-Bromo-4-fluoro-3-methyl-2-nitrophenol (16c)

[00316] To a solution of **16b** (14 g, 68.3 mmol) in DCM (150 mL) was added nitric acid (3.2 mL, 81.9 mmol, 68%) under nitrogen at -20 °C. The reaction mixture was stirred at -20 °C for 2 h. The reaction was quenched with H_2O (50 mL) and extracted with EA (200 mL*3). The combined organic layer was washed by brine (200 mL*2), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (PE) to give **16c** (9.5 g, 55% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 2.48 (s, 3H). LC-MS (ESI, Method 2), t_R = 2.58 min, m/z (^{79}Br, $M+H)^+$ = 250.0.

Step 3. 1-Bromo-5-fluoro-2-methoxy-4-methyl-3-nitrobenzene (16d)

[00317] To a solution of **16c** (5 g, 20.0 mmol) in DCM (50 mL) stirred under nitrogen at 25 °C was added a solution of CH_3I (3.41 g, 0.024 mol, 1.49 mL) and K_2CO_3 (8.29 g, 60.0 mmol). The reaction mixture was stirred at 25 °C for 16 h. The reaction was then quenched by water (100 mL), extracted with ethyl acetate (100 mL), washed with water (100 mL*2) and brine (100 mL*2), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (EA in PE is 10-30%) to afford **16d** (4.9 g, 92% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 2.18(s, 3H).

Step 4. 2-(4-Bromo-6-fluoro-3-methoxy-2-nitrophenyl)-*N*,*N*-dimethylethen-1-amine (16e)

[00318] To a solution of **16d** (2 g, 7.6 mmol) in DMF (9 mL) was added DMF-DMA (20 mL, 22.8 mmol) under nitrogen atmosphere at 25 °C. The resulting solution was stirred at 110 °C for 3 h under nitrogen atmosphere. The solvent was evaporated under vacuum to give **16e** (2.1 g, crude) as a yellow oil, which was used for the next step directly without further purification.

Step 5. 6-Bromo-4-fluoro-7-methoxy-1*H*-indole (16f)

[00319] To a solution of **16e** (2 g, 6.3 mmol) in EtOH/HOAc = 1/1 (40 mL) was added Fe powder (1.06 g, 18.9 mmol) under nitrogen at 25 °C. The reaction mixture was stirred at 80 °C for 2 h. The reaction was then quenched by water (50 mL), extracted with EtOAc (100 mL*2), washed with water (100 mL*2) and brine (100 mL*2), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (EA in PE is 10-40%) to afford **16f** (550 mg, 33% yield) as a yellow oil. LC-MS (ESI, Method 4), t_R = 2.75 min, m/z (^{79}Br, M-H)$^-$ = 242.0.

Step 6. 6-Bromo-1-ethyl-4-fluoro-7-methoxy-1*H*-indole (16g)

[00320] To a solution of **16f** (700 mg, 2.88 mmol) in DMF (10 mL) stirred under nitrogen at 0 °C was added NaH (127 mg, 3.17 mmol, 60% in mineral oil). The reaction mixture was stirred at 0 °C for 0.5 h. To the mixture was added C_2H_5I (494 mg, 3.17 mmol, 2.5 mL). The mixture was stirred at 70 °C for 16 h. After cooling to room temperature, the reaction was quenched by water (50 mL), extracted with EA (100 mL*2), washed with water (100 mL*2) and brine (100 mL*2), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **16g** (500 mg, 64% yield) as a

yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 3.2 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).

Step 7. Methyl 6-(cyclopropanecarboxamido)-4-((1-ethyl-4-fluoro-7-methoxy-1*H*-indol-6-yl)amino)nicotinate (16h)

[00321] To a solution of **16g** (500 mg, 1.84 mmol) in dioxane (5 mL) was added Cs_2CO_3 (599 mg, 5.52 mmol), EPhos Pd G4 (169 mg, 0.18 mmol), EPhos (196 mg, 0.37 mmol) and **Int. D** (642 mg, 1.84 mmol). The reaction mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The mixture was cooled to room temperature, diluted with water (10 mL) and extracted with EtOAc (15 mL*3). The combined organic layer was washed by brine (20 mL*2), dried over sodium sulphate and evaporated in vacuo. The residue was purified by *prep*-TLC (DCM/MeOH = 20/1) to give **16h** (180 mg, 22% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.74 min, m/z $(M+H)^+$ = 427.1.

Step 8. 6-(Cyclopropanecarboxamido)-4-((1-ethyl-4-fluoro-7-methoxy-1*H*-indol-6-yl)amino)nicotinic acid (16i)

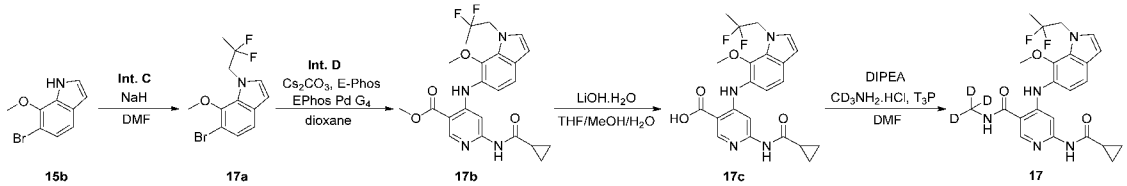
[00322] To a solution of **16h** (180 mg, 0.42 mmol) in THF (1.2 mL), MeOH (0.6 mL) and H_2O (0.4 mL) was added LiOH.H_2O (36 mg, 0.846 mmol) and stirred at 40 °C for 16 h under N_2 atmosphere. The mixture was diluted with water (5 mL), adjusted to pH = 2 with 2 N HCl and extracted with EtOAc (5 mL*3). The combined organic layer was washed by brine (5 mL*2), dried over sodium sulphate and evaporated in vacuo. The residue was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **16i** (150 mg, 86% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.61 min, m/z $(M+H)^+$ = 413.1.

Step 9. 6-(Cyclopropanecarboxamido)-4-((1-ethyl-4-fluoro-7-methoxy-1*H*-indol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (16)

[00323] To a solution of **16i** (150 mg, 0.35 mmol) in DMF (2 mL) was added CD_3NH_2.HCl (39 mg, 0.53 mmol), EDCI (82 mg, 0.42 mmol), HOBt (60 mg, 0.42 mmol) and TEA (221 mg, 2.1 mmol, 0.3 mL). The reaction mixture was stirred at 25 °C for 16 h under N_2 atmosphere. The mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layer was washed by brine (5 mL*2), dried over sodium sulphate, evaporated in vacuo and purified by *prep*-TLC (DCM/MeOH = 10/1) to give the crude product (30 mg). Then the

crude product was purified by *prep*-HPLC (Method F) to give **16** (10 mg, 6% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 10.42 (s, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 7.77 (s, 1H), 7.40 (d, J = 3.2 Hz, 1H), 6.78 (d, J = 10.8 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 1.94-1.93 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 0.73-0.71 (m, 4H). LC-MS (ESI, Method 4), t_R = 3.07 min, m/z $(M+H)^+$ = 429.1.

Example 17



Step 1. 6-Bromo-1-(2,2-difluoropropyl)-7-methoxy-1*H*-indole (17a)

[00324] To a solution of **15b** (1.5 g, 6.6 mmol) in DMF (15 mL) was added NaH (400 mg, 9.9 mmol, 60% in mineral oil) and **Int. C** (700 mg, 9.9 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 3 h under N_2 atmosphere. 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 Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **17a** (830 mg, 37% yield) as a yellow solid. LC-MS ((ESI, Method 2), t_R = 2.24 min, m/z (^{79}Br, $M+H)^+$ = 303.8.

Step 2. Methyl 6-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-indol-6-yl)amino)nicotinate (17b)

[00325] To a solution of **17a** (800 mg, 2.63 mmol) in dioxane (6 mL) was added **Int. D** (918 mg, 2.63 mmol), Cs_2CO_3 (2.57 g, 7.89 mmol), EPhos (280.9 mg, 0.526 mmol) and EPhos Pd G4 (241.6 mg, 0.263 mmol). The reaction mixture was stirred at 90 °C under N_2 atmosphere for 16 h. The mixture was cooled to room temperature and diluted with water (30 mL), extracted with EA (50 mL*3). The combined organic layer was washed by brine (50 mL*2), dried over sodium sulphate and evaporated in vacuo. The residue was purified by *prep*-TLC (DCM/MeOH = 20/1) to give **17b** (120 mg, 6% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.65 min, m/z $(M+H)^+$ = 459.1.

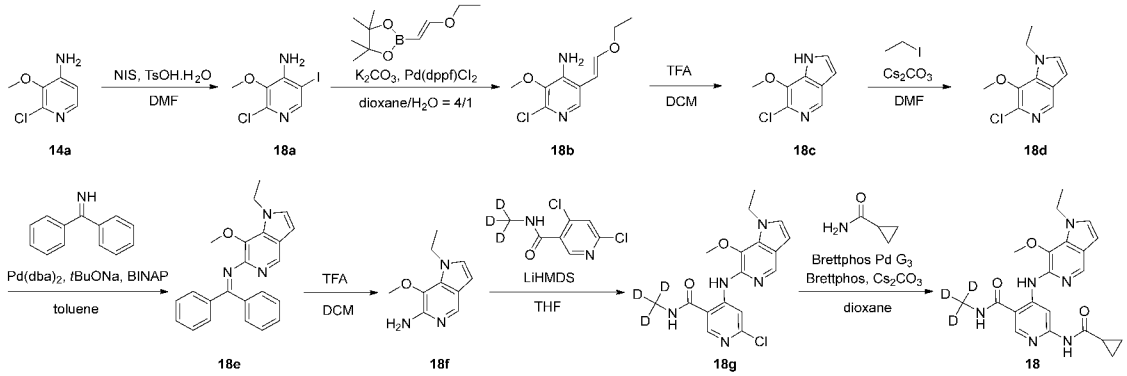
Step 3. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-indol-6-yl)amino)nicotinic acid (17c)

[00326] To a solution of **17b** (110 mg, 0.239 mmol) in THF/MeOH/H_2O = 3/2/1 (2 mL) was added LiOH.H_2O (20.1 mg, 0.479 mmol). The resulting mixture was stirred at 40 °C for 16 h under N_2 atmosphere. The mixture was diluted with water (20 mL) and extracted with EA (2 mL*3). The combined organic layer was washed by brine (2 mL*2), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (MeOH in DCM is 10-50%) to give **17c** (55 mg, 41% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.59 min, m/z $(M+H)^+$ = 445.0.

Step 4. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-indol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (17)

[00327] A mixture of CD_3NH_2·HCl (16.4 mg, 0.234 mmol), **7** (35 mg, 0.078 mmol), DIPEA (30.5 mg, 0.236 mmol, 0.158 mL) and T_3P (148.8 mg, 0.234 mmol, 50% purity in EtOAc) in DMF (2 mL) was stirred at 70 °C for 12 h. A yellow solution was formed. The reaction mixture was diluted with water (10 mL), then extracted with EtOAc (1 mL*2). The combined organic layer was washed with water (1 mL) and brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC (Method E) to give **17** (3.1 mg, 8% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.34 (s, 1H), 8.55 (s, 1H), 8.49 (s, 1H), 7.69 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 3.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 4.81 (q, J = 14.4 Hz, 2H), 3.72 (s, 3H), 1.92-1.90 (m, 1H), 1.58 (t, J = 18.8 Hz, 3H), 0.70-0.72 (m, 4H). LC-MS (ESI, Method 4), t_R = 2.79 min, m/z $(M+H)^+$ = 461.1.

Example 18



Step 1. 2-Chloro-5-iodo-3-methoxypyridin-4-amine (18a)

[00328] To a solution of **14a** (2 g, 12.6 mmol) in DMF (10 mL) was added NIS (4.25 g, 18.9 mmol) and $TsOH{\cdot}H_2O$ (240 mg, 1.2 mmol). The mixture was stirred for 12 h at 70 °C. The mixture was quenched with water (50 mL), extracted with EA (50 mL*3), dried over Na_2SO_4 and concentrated to give crude product **18a**. The residue was purified by flash chromatography (EA in PE is 5-15%) to give **18a** (3.4 g, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 6.33 (s, 2H), 3.70 (s, 3H). LC-MS (ESI, Method 2), t_R = 1.52 min, m/z $(M+H)^+$ = 284.9.

Step 2. (*E*)-2-chloro-5-(2-ethoxyvinyl)-3-methoxypyridin-4-amine (18b)

[00329] To a solution of **18a** (3.4 g, 12 mmol) in dioxane/H_2O = 4/1 (14 mL) was added (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.85 g, 14.4 mmol), K_2CO_3 (4.98 g, 3.6 mmol) and $Pd(dppf)Cl_2$ (1.76 g,2.4 mmol). The mixture was stirred for 16 h at 60 °C. The mixture was quenched with water (50 mL), extracted with EtOAc (50 mL*3), dried over Na_2SO_4 and concentrated to give crude product **18b**. The residue was purified by flash chromatography (EA in PE is 10-20%) to give **18b** (2.56 g, 88% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.74 (s, 1H), 6.75 (d, *J* = 12.8 Hz, 1H), 5.51 (d, *J* = 12.8 Hz, 1H), 4.44 (s, 2H), 3.92 (q, *J* = 7.2 Hz, 3H), 3.85 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI, Method 2), t_R = 1.27 min, m/z $(M+H)^+$ = 229.1.

Step 3. 6-Chloro-7-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine (18c)

[00330] To a solution of **18b** (2.56 g, 11.2 mmol) in DCM (20 mL) was added TFA (5 mL).The mixture was stirred for 2 h at 25 °C. The mixture was concentrated. The residue was dissolved with water, adjusted to pH = 7 with *aq.* $NaHCO_3$, extracted with DCM (10 mL*3),

dried over Na_2SO_4 and concentrated to give **18c** (2 g, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 2), t_R = 0.20 min, m/z $(M+H)^+$ = 183.0.

Step 4. 6-Chloro-1-ethyl-7-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine (18d)

[00331] To a solution of **18c** (1 g, 5.50 mmol) and iodoethane (1.29 g, 8.25 mmol) in DMF(10 mL) stirred at 25 °C was added Cs_2CO_3 (1.52 g, 11 mmol). The reaction mixture was stirred at 70 °C for 16 h. 30 mL of water was added to the mixture. The mixture was extracted with EtOAc (50 mL*3). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EA in PE is 10-30%) to give **18d** (650 mg, crude), which was used for the next step directly without further purification. LC-MS (ESI, Method 2), t_R = 1.54 min, m/z $(M+H)^+$ = 211.0.

Step 5. *N*-(1-ethyl-7-methoxy-1*H*-pyrrolo[3,2-*c*] pyridin-6-yl)-1,1-diphenylmethanimine (18e)

[00332] To a solution of **18d** (600 mg, 2.85 mmol), diphenylmethanimine (1.55 g, 8.54 mmol) and BINAP (709.4 mg, 1.14 mmol) in toluene (15 mL) stirred at 25 °C was added $Pd_2(dba)_3$ (522.1 mg, 0.57mmol) and *t*-BuONa (821.1 mg, 8.54 mmol). The reaction mixture was stirred at 110 °C for 16 h. Water (40 mL) was added to the mixture. The mixture was extracted with DCM (30 mL*3). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by *prep*-TLC (PE/EA = 3/1) to give **18e** (500 mg, 46% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.65 min m/z $(M+H)^+$ = 356.1.

Step 6. 1-Ethyl-7-methoxy-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (18f)

[00333] To a solution of **18e** (500 mg, 1.41 mmol) in DCM (10 mL) stirred at 25 °C was added TFA (3 mL). The reaction mixture was stirred at 25 °C for 16 h. The reaction was quenched with *aq.* $NaHCO_3$ (15 mL), extracted with DCM (30 mL*3). The combined organic layer was washed by brine (5 mL), dried over sodium sulphate and evaporated in vacuo. The residue was purified by *prep*-TLC with (DCM/MeOH = 10/1) to give **18f** (170 mg, 61% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.16 (d, J = 3.2 Hz, 1H), 6.39 (d, J = 3.2 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). LC-MS (ESI, Method 2), t_R = 1.13 min, m/z $(M+H)^+$ = 192.1.

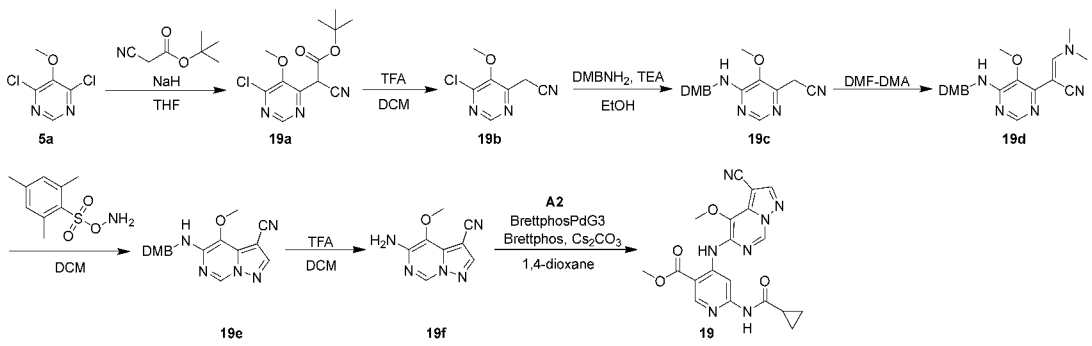
Step 7. 6-Chloro-4-((1-ethyl-7-methoxy-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (18g)

[00334] To a solution of **18f** (70 mg, 0.37 mmol) and 4,6-dichloro-*N*-(methyl-d_3)nicotinamide (152.3 mg, 0.73 mmol) in THF (7 mL) stirred at 0 °C was added LiHMDS (1.84 mL, 1 mol/L in THF) dropwise. The reaction mixture was stirred at 0 °C for 4 h. A solution of *sat.* NH_4Cl (2 mL) was added to the mixture. The reaction was extracted with DCM (15 mL*3). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **18g** (100 mg, 75% yield) as a yellow solid. LC-MS (ESI, Method 2), t_R = 1.36 min, m/z $(M+H)^+$ = 363.0.

Step 8. 6-(Cyclopropanecarboxamido)-4-((1-ethyl-7-methoxy-1*H*-pyrrolo[3,2-*c*] pyridin-6-yl) amino)-*N*-(methyl-d_3)nicotinamide (18)

[00335] To a mixture of **18g** (100 mg, 0.28 mmol), cyclopropanecarboxamide (117.3 mg, 1.38 mmol) and Cs_2CO_3 (179.6 mg, 0.55 mmol) in dioxane (10 mL) stirred under nitrogen at 25 °C was added BrettPhos (29.6 mg, 0.055 mmol), BrettPhos Pd G3 (25.0 mg, 0.027 mmol). The reaction mixture was stirred at 90 °C for 16 h. Water (20 mL) was added to the mixture. The mixture was extracted with EA (30 mL*2). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by *prep*-TLC (DCM/MeOH = 10/1) to give **18** (30 mg, crude). The crude product was purified by *prep*-HPLC (Method E) to give **18** (9.5 mg, 8% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 10.62 (s, 1H), 9.02 (s, 1H), 8.58 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 7.38 (d, J = 3.2 Hz, 1H), 6.55 (d, J = 3.2 Hz, 1H), 4.38-4.31 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.02-1.95 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 0.80-0.74 (m, 4H). LC-MS (ESI, Method 4), t_R = 2.45 min, m/z $(M+H)^+$ = 412.2.

Example 19



Step 1. *Tert*-butyl 2-(6-chloro-5-methoxypyrimidin-4-yl)-2-cyanoacetate (19a)

[00336] To a solution of *tert*-butyl 2-cyanoacetate (9.46 g, 67.04 mmol) in THF (200 mL) was added NaH (5.36 g, 134.08 mmol, 60% in mineral oil) at 0 °C. After stirring at 0 °C for 30 min, to it was added a solution of **5a** (10 g, 55.86 mmol) in THF (20 mL). The mixture was stirred at 80 °C for 2 h. After cooling to r.t., the reaction mixture was poured into ice-water (150 mL) and acidified with 2 N HCl to pH = 2. The mixture was extracted with EtOAc (300 mL*2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered. The filtrate was concentrated under reduced pressure to afford **19a** (15 g, 95% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.13 min, m/z $(M+H-56)^+$ = 228.2.

Step 2. 2-(6-Chloro-5-methoxypyrimidin-4-yl)acetonitrile (19b)

[00337] To a mixture of **19a** (7.5 g, 26.44 mmol) in DCM (100 mL) was added TFA (50 mL) at 0 °C. The mixture was stirred at r.t. for 4 h. The solvent was concentrated. The residue was diluted with H_2O (100 mL), adjusted to pH = 9 with saturated Na_2CO_3 solution and extracted with EtOAc (100 mL*3). The combined organic layer was concentrated under reduced pressure to afford **19b** (4.8 g, 99% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 4.05 (s, 3H), 3.97 (s, 2H).

Step 3. 2-(6-((2,4-Dimethoxybenzyl)amino)-5-methoxypyrimidin-4-yl)acetonitrile (19c)

[00338] A mixture of **19b** (4.8 g, 26.14 mmol), TEA (7.3 mL, 52.3 mmol) and $DMBNH_2$ (5.68 g, 33.99 mmol) in EtOH (30 mL) was stirred at 80 °C for 2 h. After cooling to r.t., the mixture was diluted with H_2O (40 mL) and extracted with EtOAc (80 mL*2). The combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to afford **19c** (5.35 g, 65% yield) as a yellow oil. LC-MS (ESI, Method 3) t_R = 0.99 min, m/z $(M+H)^+$ = 315.3.

Step 4. (*Z*)-2-(6-((2,4-dimethoxybenzyl)amino)-5-methoxypyrimidin-4-yl)-3-(dimethylamino)acrylonitrile (19d)

[00339] A mixture of **19c** (5.35 g, 17.02 mmol) in DMF-DMA (35 mL) was stirred at 130 °C for 10 h. The mixture was cooled and concentrated under reduced pressure to afford **19d** (6.29 g, yield given) as a yellow oil. LC-MS (ESI, Method 3) t_R = 1.06 min, m/z $(M+H)^+$ = 370.2.

Step 5. 5-((2,4-Dimethoxybenzyl)amino)-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carbonitrile (19e)

[00340] To a mixture of **19d** (3.0 g, 8.12 mmol) in DCM (50 mL) was added dropwise a solution of *O*-(mesitylsulfonyl)hydroxylamine (2.10 g, 9.75 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. Another batch of *O*-(mesitylsulfonyl)hydroxylamine (0.58 g, 2.69 mmol) in DCM (5 mL) was added to the reaction mixture at 0 °C. The mixture was stirred at r.t. for 18 h and purified by flash chromatography on silica gel (DCM/EA = 20/1) to afford **19e** (730 mg, 26% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.03 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 5.56 (s, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.76 (s, 3H).

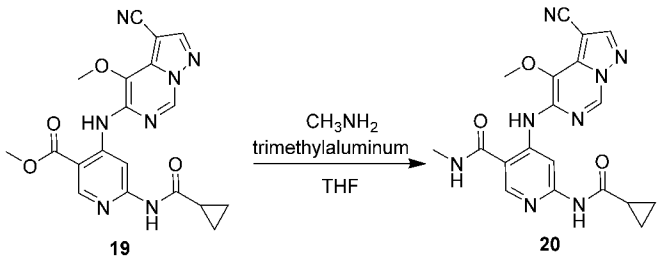
Step 6. 5-Amino-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carbonitrile (19f)

[00341] To a solution of **19e** (400 mg, 1.18 mmol) in DCM (2 mL) was added TFA (2 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 H_2O (80 mL) and the solution was adjusted to pH = 12 with 1 M NaOH solution. The mixture was extracted with DCM (80 mL*3). The combined organic layer was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to afford **19f** (100 mg, 44% yield) as a yellow solid. LC-MS (ESI, Method 2) t_R = 0.60 min, m/z $(M+H)^+$ = 190.2.

Step 7. Methyl 4-((3-cyano-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-6-(cyclopropanecarboxamido)nicotinate (19)

[00342] A mixture of **19f** (100 mg, 0.53 mmol), **A2** (148 mg, 0.58 mmol), BrettPhos Pd G3 (48 mg, 0.053 mmol), BrettPhos (28 mg, 0.053 mmol) and Cs_2CO_3 (344 mg, 1.06 mmol) in 1,4-dioxane (1 mL) was stirred at 90 °C overnight under N_2 atmosphere. After cooling to r.t., the mixture was concentrated. And the residue was purified by flash chromatography on silica gel (DCM/EA = 20/1) to afford **19** (58 mg, 27% yield) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 9.36 (s, 1H), 8.81 (s, 1H), 8.71 (s, 1H), 4.03 (s, 3H), 3.92 (s, 3H), 2.07-2.04 (m, 1H), 0.85-0.81 (m, 4H). LC-MS (ESI, Method 2) t_R = 1.60 min, m/z $(M+H)^+$ = 408.2.

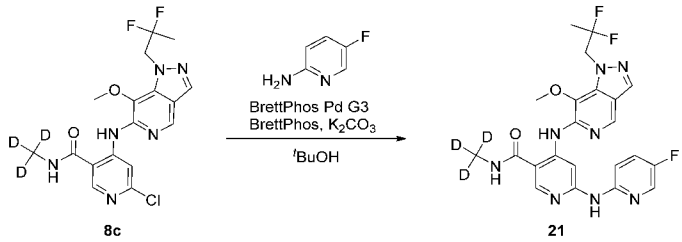
Example 20



Step 1. 4-((3-Cyano-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-6-(cyclopropanecarboxamido)-*N*-methylnicotinamide (20)

[00343] To a solution of **19** (100 mg, 0.25 mmol) and CH_3NH_2 (2.45 mL, 2.45 mmol, 1 M in THF) in THF (4 mL) was slowly added trimethylaluminum (1.23 mL, 1.23 mmol, 1 M in petroleum ether) dropwise. The reaction was stirred at 70 °C for 5 h. After cooling to r.t., the reaction was quenched with H_2O (1 mL), adjusted to pH = 6 with 2 M HCl and extracted with EtOAc (5 mL*2). The organic layer was separated, concentrated and the residue was purified by *prep*-HPLC (Method A) to afford **20** (6 mg, 6% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 10.86 (s, 1H), 9.54 (s, 1H), 9.26 (s, 1H), 8.81 (s, 1H), 8.68 (s, 1H), 8.65 (s, 1H), 4.00 (s, 3H), 2.84 (d, J = 4.4 Hz, 3H), 2.05-1.98 (m, 1H), 0.86-0.83 (m, 4H). LC-MS (ESI, Method 2) t_R = 2.60 min, m/z $(M+H)^+$ = 407.1.

Example 21

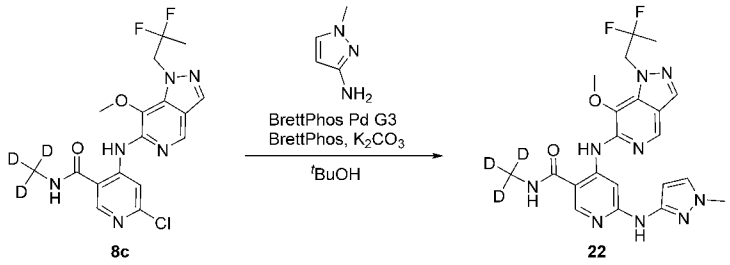


Step 1. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-6-((5-fluoropyridin-2-yl)amino)-*N*-(methyl-d_3)nicotinamide (21)

[00344] To a solution of **8c** (30 mg, 0.072 mmol), 5-fluoropyridin-2-amine (12 mg, 0.11 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in ^{t}BuOH (2 mL) was added BrettPhos Pd G3 (10 mg, 0.011 mmol) and BrettPhos (10 mg, 0.019 mmol) under N_2 atmosphere. The mixture was stirred at 110 °C for 5 h. The reaction mixture was diluted with water (20 mL), then extracted with EtOAc (20 mL*2). The combined organic layer was washed with brine (20 mL*2), dried over

anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC (Method E) to give **21** (12 mg, 34% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 9.87 (s, 1H), 9.02 (s, 1H), 8.76 (s, 1H), 8.56 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.25 (d, J = 2.8 Hz, 1H), 7.78-7.72 (m, 1H), 7.68-7.61 (m, 1H), 4.93 (t, J = 13.2 Hz, 2H), 3.91 (s, 3H), 1.71 (t, J = 19.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.32 min, m/z $(M+H)^+$ = 490.3.

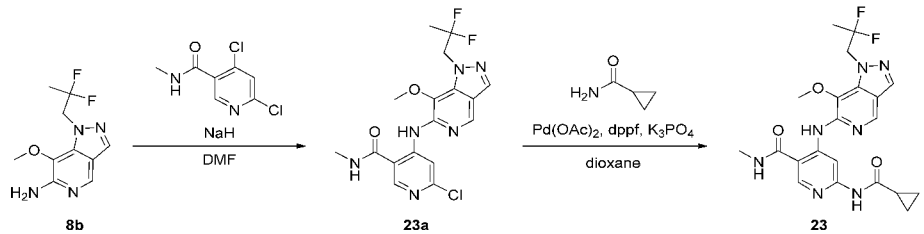
Example 22



Step 1. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-*d*3)-6-((1-methyl-1*H*-pyrazol-3-yl)amino)nicotinamide (22)

[00345] To a solution of **8c** (30 mg, 0.072 mmol), 1-methyl-1*H*-pyrazol-3-amine (11 mg, 0.11 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in ^{t}BuOH (2 mL) was added BrettPhos Pd G3 (10 mg, 0.011 mmol) and BrettPhos (10 mg, 0.019 mmol) under N_2 atmosphere. The mixture was stirred at 110 °C for 2 h. The reaction mixture was diluted with water (20 mL), then extracted with EtOAc (20 mL*2). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC (Method E) to give **22** (21 mg, 60% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 9.32 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.47-8.44 (m, 2H), 8.33 (s, 1H), 7.53 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 4.93 (t, J = 13.2 Hz, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 1.70 (t, J = 19.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.08 min, m/z $(M+H)^+$ = 475.4.

Example 23



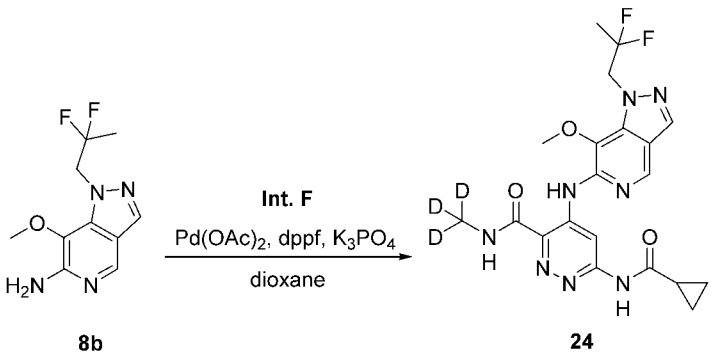
Step 1. 6-Chloro-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-methylnicotinamide (23a)

[00346] To a solution of **8b** (60 mg, 0.25 mmol) in DMF (4 mL) was added NaH (40 mg, 0.99 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred for 30 min, then 4,6-dichloro-*N*-methylnicotinamide (66 mg, 0.32 mmol) was added. The mixture was stirred at room temperature for 12 h. The mixture was quenched with *sat.* NH_4Cl (20 mL) and extracted with EtOAc (20 mL*2). The combined organic layer was washed with brine (15 mL*2), dried and condensed by vacuum. The residue was purified by flash chromatography (EtOAc in DCM is 65%) to give **23a** (53 mg, 52% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.81 min, m/z $(M+H)^+$ = 411.2.

Step 2. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-methylnicotinamide (23)

[00347] To a solution of **23a** (20 mg, 0.049 mmol) and cyclopropanecarboxamide (17 mg, 0.19 mmol) in dioxane (2 mL) was added $Pd(OAc)_2$ (2 mg, 0.009 mmol), dppf (11 mg, 0.019 mmol) and K_3PO_4 (31 mg, 0.015 mmol) under N_2 atmosphere. The mixture was stirred at 100 °C for 3 h. The reaction mixture was diluted with water (20 mL), then extracted with EtOAc (20 mL*2). The combined organic layer was washed with brine (20 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC (Method E) to give **23** (6 mg, 29% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 10.73 (s, 1H), 9.22 (s, 1H), 8.76-8.64 (m, 2H), 8.56 (s, 1H), 8.32 (s, 1H), 4.93 (t, J = 13.2 Hz, 2H), 3.89 (s, 3H), 2.82 (d, J = 4.4 Hz, 3H), 2.05-1.97 (m, 1H), 1.70 (t, J = 19.2 Hz, 3H), 0.84-0.76 (m, 4H). LC-MS (ESI, Method 4) t_R = 1.97 min, m/z $(M+H)^+$ = 460.3.

Example 24

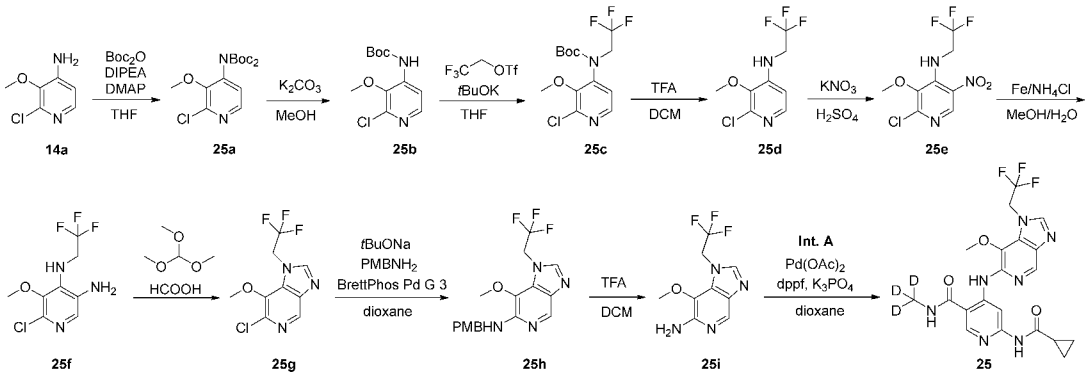


8b **24**

Step 1. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)pyridazine-3-carboxamide (24)

[00348] To a solution of **8b** (10 mg, 0.041 mmol), **Int. F** (16 mg, 0.062 mmol), dppf (9 mg, 0.017 mmol), K_3PO_4 (26 mg, 0.12 mmol) in dioxane (3 mL) was added $Pd(OAc)_2$ (2 mg, 0.008 mmol) at r.t.. The reaction was stirred at 100 °C for 6 h under nitrogen protection. The reaction was added into H_2O (10 mL) and extracted by EtOAc (20 mL). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography and *prep*-HPLC (Method E) to afford **24** (1.5 mg, 8% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 11.32 (s, 1H), 9.63 (s, 1H), 9.26 (s, 1H), 8.73 (s, 1H), 8.36 (s, 1H), 4.94 (t, J = 12.8 Hz, 2H), 3.93 (s, 3H), 2.18-2.08 (m, 1H), 1.70 (t, J = 19.2 Hz, 3H), 0.91-0.83 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.13 min, m/z $(M+H)^+$ = 464.3.

Example 25



Step 1. *Tert*-butyl *N*-[(*tert*-butoxy)carbonyl]-*N*-(2-chloro-3-methoxypyridin-4-yl)carbamate (25a)

[00349] To a solution of **14a** (3 g, 18.92 mmol), DMAP (2.31 g, 18.92 mmol), DIPEA (4.89 g, 37.83 mmol, 6.59 mL) in THF (50 mL) was added Boc_2O (8.26 g, 8.68 mL) at an ice-bath, then the mixture was stirred at r.t. overnight. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (100 mL*3), washed with brine (100 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated to get the crude compound **25a** (6.79 g, yield given) as a white solid. LC-MS (ESI, Method 4) t_R = 3.44 min, m/z $(M+H)^+$ = 359.3.

Step 2. *Tert*-butyl (2-chloro-3-methoxypyridin-4-yl)carbamate (25b)

[00350] To a solution of **25a** (6.79 g, 18.92 mmol) in MeOH (70 mL) was added K_2CO_3 (13.08 g, 94.62 mmol). Then the mixture was stirred at 70 °C for 4 h. The mixture was concentated and diluted with H_2O (100 mL), extracted with EtOAc (50 mL*3), washed with brine (50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated and purifed by flash chromatography (PE/EA = 20/1 to 1/1) to get compound **25b** (4.0 g, 82% yield) as a white solid. LC-MS (ESI, Method 4) t_R = 2.97 min, m/z $(M+H)^+$ = 259.1.

Step 3. *Tert*-butyl (2-chloro-3-methoxypyridin-4-yl)(2,2,2-trifluoroethyl)carbamate (25c)

[00351] To a solution of **25b** (500 mg, 1.93 mmol) in THF (5 mL) was added ^{t}BuOK (281 mg, 2.51 mmol), then the mixture was stirred at 60 °C for 30 min. Then 2,2,2-trifluoroethyl trifluoromethanesulfonate (583 mg, 2.51 mmol) was added into the mixture and stirred at 60 °C for 2 h. Then the mixture was cooled to r.t. and another batch of ^{t}BuOK (281 mg, 2.51 mmol) was added. Then the mixture was stirred at 60 °C for 30 min. Then 2,2,2-trifluoroethyl trifluoromethanesulfonate (583 mg, 2.51 mmol) was added into the mixture and stirred at 60 °C for 2 h. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL*3), washed with brine (30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated to get the crude compound **25c** (500 mg, 76% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 3.37 min, m/z $(M+H)^+$ = 341.2.

Step 4. 2-Chloro-3-methoxy-*N*-(2,2,2-trifluoroethyl)pyridin-4-amine (25d)

[00352] To a solution of **25c** (500 mg, 1.47 mmol) in DCM (5 mL) was added TFA (2.24 g, 19.60 mmol, 1.5 mL), then the mixture was stirred at r.t. for 4 h. The mixture was concentrated and diluted with H_2O (10 mL), adjusted to pH > 7 with *aq.* Na_2CO_3, extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated and purified by flash chromatography (PE/EA = 20/1 to 2/1) to get compound **25d** (233 mg, 66% yield) as a white solid. LC-MS (ESI, Method 4) t_R = 2.07 min, m/z $(M+H)^+$ = 241.0.

Step 5. 2-Chloro-3-methoxy-5-nitro-*N*-(2,2,2-trifluoroethyl)pyridin-4-amine (25e)

[00353] To a solution of **25d** (200 mg, 0.83 mmol) in *conc.* H_2SO_4 (2 mL) was added KNO_3 (109 mg, 1.08 mmol) at 0 °C, then the mixture was stirred at r.t. for 6 h. The mixture was added into the ice-water dropwise, then basified to pH > 9 with $NH_3.H_2O$, extracted with EtOAc (15 mL*4), washed with brine (20 mL), dried over Na_2SO_4 and concentrated to get compound **25e**

(160 mg, 67% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.93 min, m/z $(M+H)^+$ = 286.0.

Step 6. 6-Chloro-5-methoxy-*N*^{4}-(2,2,2-trifluoroethyl)pyridine-3,4-diamine (25f)

[00354] A mixture of **25e** (160 mg, 0.56 mmol), Fe powder (156 mg, 2.80 mmol), NH_4Cl (150 mg, 2.80 mmol) in MeOH (2 mL) and H_2O (0.5 mL) was stirred at 70 °C for 2 h. The mixture was filtered and the filter cake was washed with EtOAc (10 mL*2). The filtrate was concentrated and diluted with H_2O (10 mL), basified by $NH_3.H_2O$ to pH > 13, extracted with EtOAc (10 mL*3), washed with brine (10 mL), dried over Na_2SO_4, concentrated to get compound **25f** (130 mg, 91% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.09 min, m/z $(M+H)^+$ = 256.1.

Step 7. 6-Chloro-7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-imidazo[4,5-*c*]pyridine (25g)

[00355] To a solution of **25f** (130 mg, 0.51 mmol) in trimethoxymethane (2 mL) was added HCOOH (0.1 mL), then the mixture was stirred at 105 °C for 4 h. The mixture was concentrated, diluted with H_2O (20 mL), extracted with EtOAc (15 mL*3), washed with brine (15 mL), dried over Na_2SO_4 and concentrated to get the crude compound **25g** (130 mg, 96% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.24 min, m/z $(M+H)^+$ = 266.0.

Step 8. 7-Methoxy-*N*-(4-methoxybenzyl)-1-(2,2,2-trifluoroethyl)-1*H*-imidazo[4,5-*c*]pyridin-6-amine (25h)

[00356] A mixture of **25g** (120 mg, 0.45 mmol), (4-methoxyphenyl)methanamine (124 mg, 0.90 mmol), BrettPhos Pd G3 (82 mg, 0.09 mmol), *t*BuONa (108 mg, 1.13 mmol) in dioxane (1.5 mL) was stirred at 90 °C for 2 h. The mixture was concentrated and purified by flash chromatography (DCM/MeOH = 100/1 to 20/1) to get compound **25h** (150 mg, 90% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.24 min, m/z $(M+H)^+$ = 367.2.

Step 9. 7-Methoxy-1-(2,2,2-trifluoroethyl)-1*H*-imidazo[4,5-*c*]pyridin-6-amine (25i)

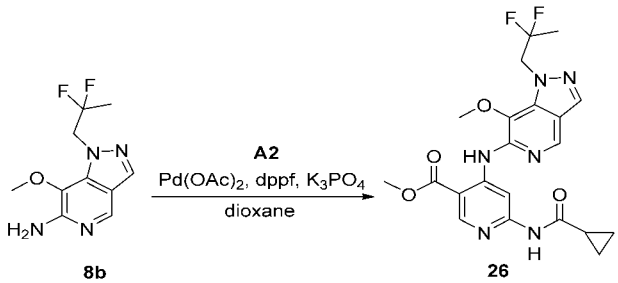
[00357] To a solution of **25h** (150 mg, 0.41 mmol) in DCM (2 mL) was added TFA (2 mL), and the mixture was stirred at r.t. for 2 h. The mixture was concentrated and diluted with H_2O (20 mL), adjusted to pH > 10 with *aq.* Na_2CO_3 and extracted with EtOAc (20 mL*3). The combined organic layer was washed with brine (30 mL*2), dried over Na_2SO_4, concentrated and purified by flash chromagraphy (DCM/MeOH = 100/1 to 5/1) to get compound **25i** (57 mg, 57% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.02 (s, 1H), 5.63 (s,

2H), 5.15 (q, J = 9.2 Hz, 2H), 3.76 (s, 3H). LC-MS (ESI, Method 4) t_R = 0.44 min, m/z $(M+H)^+$ = 247.1.

Step 10. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-imidazo[4,5-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (25)

[00358] A mixture of **25i** (10 mg, 0.041 mmol), **Int. A** (10 mg, 0.041 mmol), $Pd(OAc)_2$ (0.9 mg, 0.004 mmol), dppf (4.5 mg, 0.008 mmol), K_3PO_4 (17 mg, 0.08 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 4 h. The mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **25** (6.3 mg, 33% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.71 (s, 1H), 9.15 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.54 (s, 1H), 8.33 (s, 1H), 5.28 (q, J = 9.2 Hz, 2H), 3.90 (s, 3H), 2.00-1.98 (m, 1H), 0.81-0.77 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.01 min, m/z $(M+H)^+$ = 467.3.

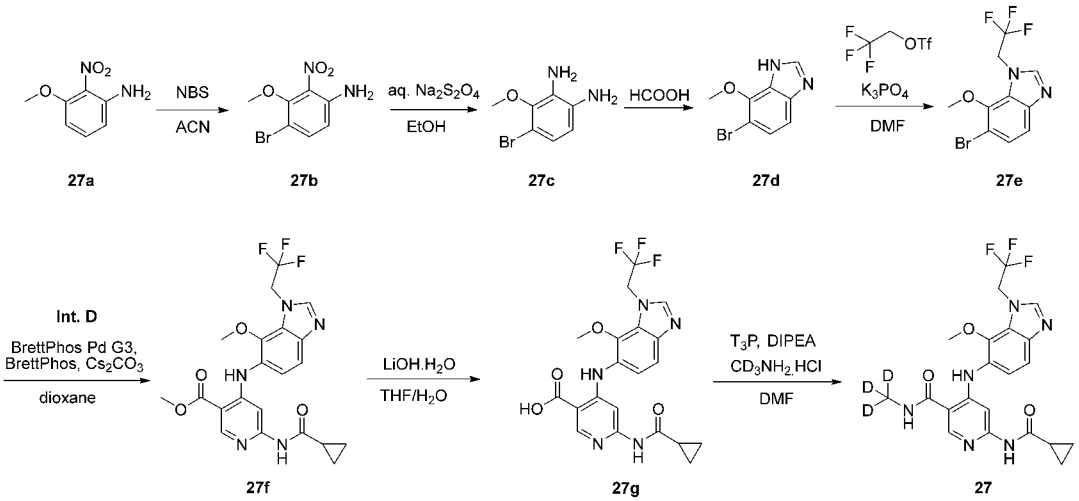
Example 26



Step 1. Methyl 6-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)nicotinate (26)

[00359] To a solution of **8b** (20 mg, 0.083 mmol), **A2** (32 mg, 0.12 mmol), dppf (18 mg, 0.033 mmol), K_3PO_4 (53 mg, 0.25 mmol) in dioxane (3 mL) was added $Pd(OAc)_2$ (4 mg, 0.017 mmol) at r.t.. The reaction was stirred at 100 °C for 6 h under nitrogen protection. The reaction was added into H_2O (10 mL) and extracted by EtOAc (20 mL). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromagraphy and *prep*-HPLC (Method E) to afford **26** (25 mg, 66% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 10.91 (s, 1H), 9.32 (s, 1H), 8.78 (s, 1H), 8.73 (s, 1H), 8.37 (s, 1H), 4.94 (t, J = 13.2 Hz, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 2.07-1.98 (m, 1H), 1.70 (t, J = 19.2 Hz, 3H), 0.84-0.80 (m, 4H). LC-MS (ESI, Method 4) t_R = 2.57 min, m/z $(M+H)^+$ = 461.3.

Example 27



Step 1. 3-Bromo-2-methoxy-6-nitro-aniline (27b)

[00360] To a solution of **27a** (3.00 g, 17.84 mmol) in ACN (30 mL) was added NBS (3.22 g, 17.84 mmol), then the mixture was stirred at r.t. for 2 h. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (50 mL*3), washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash chromatography (EA in PE is 5-20%) to give **27b** (1.35 g, 31% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 9.2 Hz, 1H), 4.96 (brs, 2H), 3.99 (s, 3H). LC-MS (ESI, Method 4) t_R = 2.76 min, m/z (^{79}Br, M+H)$^+$ = 247.0.

Step 2. 4-Bromo-3-methoxy-benzene-1,2-diamine (27c)

[00361] To a solution of **27b** (500 mg, 2.02 mmol) in EtOH (8 mL) was added aq. $Na_2S_2O_4$ (8 mL, 1 M), then the mixture was stirred at 80 °C for 2 h. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (30 mL*3), washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated to get the crude product **27c** (400 mg, 91% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 1.21 min, m/z (^{79}Br, M+H)$^+$ = 217.0.

Step 3. 6-Bromo-7-methoxy-1*H*-benzimidazole (27d)

[00362] A solution of **27c** (400 mg, 1.84 mmol) in HCOOH (5 mL) was stirred at 100 °C for 1 h. The mixture was concentrated and diluted with aq. $NaHCO_3$ (30 mL), extracted with EtOAc (30 mL*3), washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated.

The residue was purified by flash chromatography (MeOH in DCM is 0-10%) to give **27d** (370 mg, 88% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.99 min, m/z (^{79}Br, M+H)$^+$ = 227.0.

Step 4. 6-Bromo-7-methoxy-1-(2,2,2-trifluoroethyl)benzimidazole (27e)

[00363] To a solution of **27d** (100 mg, 0.44 mmol) in DMF (1.5 mL) was added K_3PO_4 (140 mg, 0.66 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (112 mg, 0.48 mmol), then the mxiture was stirred at 80 °C for 12 h. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (20 mL*3), washed with brine (40 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash chromatography (PE in EA is 10-50%) to give **27e** (40 mg, 29% yield) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.48-7.40 (m, 2H), 5.02 (q, J = 8.4 Hz, 2H), 4.04 (s, 3H). LC-MS (ESI, Method 4) t_R = 2.77 min, m/z (^{79}Br, M+H)$^+$ = 309.0.

Step 5. Methyl 6-(cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-benzo[*d*]imidazol-6-yl)amino)nicotinate (27f)

[00364] A mixture of **27e** (23 mg, 0.10 mmol), **Int. D** (35 mg, 0.10 mmol), BrettPhos Pd G3 (9 mg, 0.01 mmol), BrettPhos (11 mg, 0.02 mmol), Cs_2CO_3 (159 mg, 0.50 mmol) in dioxane (2 mL) was stirred at 100 °C for 16 h under N_2. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (10 mL*3), washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash chromatography (MeOH/DCM = 10/1) to give **27f** (25 mg, 55% yield) as a yellow soild. LC-MS (ESI, Method 4) t_R = 2.98 min, m/z (M+H)$^+$ = 464.2.

Step 6. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-benzo[*d*]imidazol-6-yl)amino)nicotinic acid (27g)

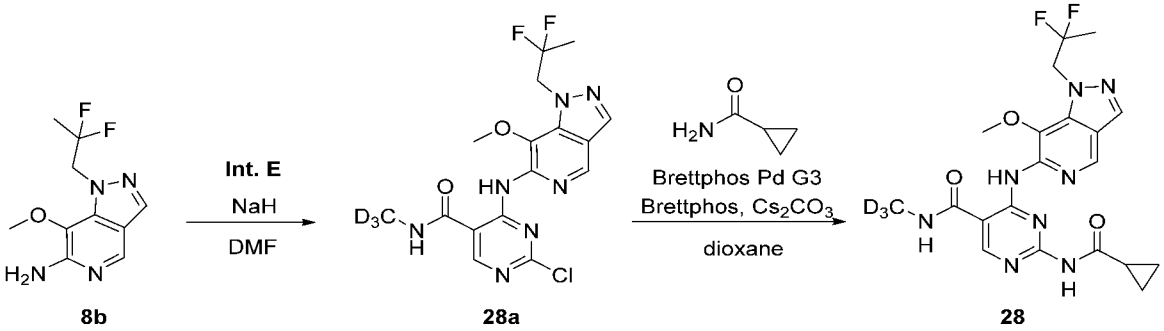
[00365] A mixture of **27f** (25 mg, 0.05 mmol) and LiOH.H_2O (7 mg, 0.15 mmol) in co-solvent of THF (2 mL) and water (1 mL) was stirred at 20 °C for 24 h. A yellow solution was formed. The reaction mixture was concentrated and dried in vacuo to give **27g** (24 mg, crude) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) t_R = 1.83 min, m/z (M+H)$^+$ = 450.2.

Step 7. 6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1*H*-benzo[*d*]imidazol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (27)

[00366] A mixture of CD_3NH_2.HCl (6 mg, 0.08 mmol), **27g** (24 mg, crude), DIPEA (21 mg,

0.16 mmol) and T_3P (52 mg, 0.08 mmol, 50% purity in EtOAc) in DMF (1 mL) was stirred at 30 °C for 3 days. A yellow solution was formed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (40 mL*3). The combined organic layer was washed with water (40 mL*3) and brine (40 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) to give **27** (5.3 mg, 21% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 10.41 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 8.26 (s, 1H), 7.70 (s, 1 H), 7.47 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 5.30 (q, J = 9.2 Hz, 2H), 3.78 (s, 3H), 1.97-1.90 (m, 1H), 0.76-0.66 (m, 4H). LC-MS (ESI, Method 4) t_R = 3.33 min, m/z $(M+H)^+$ = 466.3.

Example 28



Step 1. 2-Chloro-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)pyrimidine-5-carboxamide (28a)

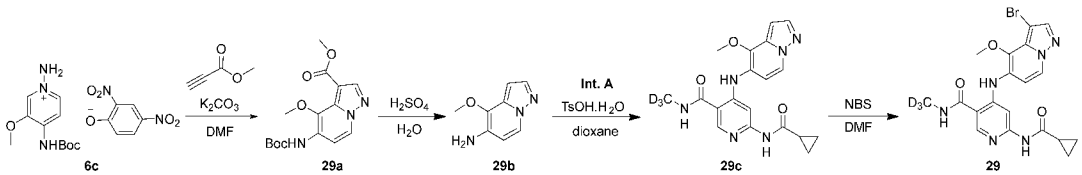
[00367] To a solution of **8b** (70 mg, 0.29 mmol) and **Int. E** (91 mg, 0.43 mmol) in DMF (10 mL) was added NaH (35 mg, 1.44 mmol, 60% in mineral oil) at 0 °C under nitrogen protection. The reaction was stirred at 0 °C to r.t. for 3 h. H_2O (10 mL) was added and the solution was extracted by EtOAc (20 mL*2). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by flash chromatography (MeOH in DCM is 1-15%) to afford **28a** (25 mg, 21% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.12 min, m/z $(M+H)^+$ = 415.2.

Step 2. 2-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-d_3)pyrimidine-5-carboxamide (28)

[00368] To a solution of **28a** (20 mg, 0.048 mmol), BrettPhos Pd G3 (9 mg, 0.01 mmol), BrettPhos (10 mg, 0.02 mmol), Cs_2CO_3 (47 mg, 0.14 mmol) in dioxane (2 mL) was added

cyclopropane carboxamide (21 mg, 0.24 mmol) at r.t.. The reaction was stirred at 100 °C for 3 h under nitrogen protection. H_2O (10 mL) was added and the solution was extracted by EtOAc (20 mL). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by *prep*-HPLC (Method E) to afford **28** (2.5 mg, 11% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 10.28 (s, 1H), 8.74 (s, 1H), 8.72 (s, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 4.98 (t, J = 13.2 Hz, 2H), 3.83 (s, 3H), 2.73-2.61 (m, 1H), 1.70 (t, J = 19.2 Hz, 3H), 0.72-0.64 (m, 2H), 0.49-0.41 (m, 2H). LC-MS (ESI, Method 4) t_R = 2.12 min, m/z $(M+H)^+$ = 464.3.

Example 29



Step 1. Methyl 5-((*tert*-butoxycarbonyl)amino)-4-methoxypyrazolo[1,5-*a*] pyridine-3-carboxylate (29a)

[00369] A mixture of methyl propiolate (749 mg, 8.91 mmol, 7.93 mL), **6c** (1.89 g, 4.45 mmol) and K_2CO_3 (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 Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (EtOAc in PE is 10-30%) to give **29a** (350 mg, 24% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 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. 4-Methoxypyrazolo[1,5-*a*]pyridin-5-amine (29b)

[00370] A mixture of **29a** (350 mg, 1.09 mmol) in *conc.* H_2SO_4/H_2O (3 mL, v/v = 1/1) was stirred at 60 °C for 2 h. After cooling to r.t., the mixture was basified with 10% aq. NaOH to pH = 9 and extracted with EtOAc (10 mL*3). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford **29b** (152 mg, 86% yield) as a black solid. LC-MS (ESI, Method 3) t_R = 0.79 min, m/z $(M+H)^+$ = 164.0.

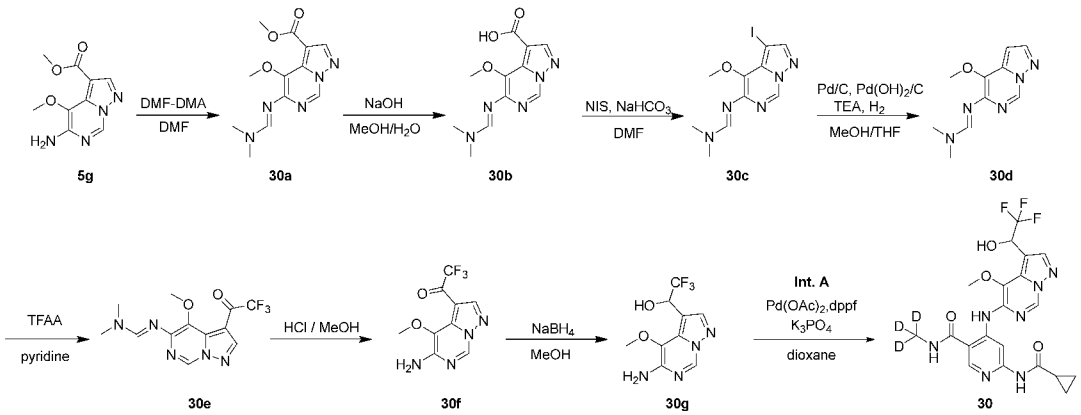
Step 3. 6-(Cyclopropanecarboxamido)-4-((4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (29c)

[00371] A solution of **29b** (150 mg, 0.92 mmol), **Int. A** (236 mg, 0.92 mmol) and TsOH.H_2O (4 mg, 0.02 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 12 h. After cooling to r.t., the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford compound **29c** (90 mg, 26% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 10.51 (s, 1H), 8.60 (s, 1H), 8.52 (s, 1H), 8.51 (d, J = 7.2 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.82 (s, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 3.92 (s, 3H), 1.98-1.95 (m, 1H), 0.76-0.74 (m, 4H). LC-MS (ESI, Method 2) t_R = 2.21 min, m/z $(M+H)^+$ = 384.1.

Step 4. 4-((3-Bromo-4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino)-6-(cyclopropanecarboxamido)-*N*-(methyl-d_3)nicotinamide (29)

[00372] To a solution of **29c** (90 mg, 0.23 mmol) in DMF (1 mL) was added NBS (50 mg, 0.28 mmol) at 0 °C. After stirring at 30 °C for 12 h, the reaction mixture was poured into H_2O (5 mL) and the formed solid was filtered. The filter cake was collected by filtration and purified by *prep*-HPLC (Method A) to afford **29** (12 mg, 11% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83(s, 1H), 10.74 (s, 1H), 8.65 (s, 1H), 8.59 (d, J = 7.6 Hz, 1H), 8.56 (s, 1H), 8.07 (s, 1H), 7.91 (s, 1H), 7.02 (d, J = 7.6 Hz, 1H), 3.82 (s, 3H), 1.99-1.96 (m, 1H), 0.78-0.75 (m, 4H). LC-MS (ESI, Method 2) t_R = 1.11 min, m/z (^{79}Br, $M+H)^+$ = 462.0.

Example 30



Step 1. Methyl 5-amino-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylate (30a)

[00373] A mixture of **5g** (6.7 g, 30.15 mmol), DMF-DMA (7.19 g, 60.31 mmol) in DMF (20 mL) was stirred at 50 °C for 4 h. The mixture was concentrated to afford **30a** (8 g, 96% yield) as a brown oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 0.73 min, m/z $(M+H)^+$ = 278.3.

Step 2. 5-(((Dimethylamino)methylene)amino)-4-methoxypyrazolo[1,5-*c*]pyrimidine-3-carboxylic acid (30b)

[00374] To a mixture of **30a** (7.5 g, 27.05 mmol) in MeOH (50 mL) and H_2O (25 mL) was added NaOH (2.16 g, 54.10 mmol). The mixture was stirred at 45 °C for 4 h and diluted with 25 mL of water. The resultant mixture was concentrated to remove organic layer and the aqueous layer was adjusted to pH = 1 with 2 M HCl. The formed solid was filtered and dried to afford **30b** (7.12 g, yield given) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.95 (s, 1H), 8.58 (s, 1H), 3.86 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H).

Step 3. *N'*-(3-iodo-4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)-*N*,*N*-dimethylformimidamide (30c)

[00375] To a solution of **30b** (4 g, 11.40 mmol) in DMF (30 mL) was added $NaHCO_3$ (1.91 g, 22.79 mmol) at 0 °C. To the reaction mixture was added NIS (5.13 g, 22.79 mmol) portionwise over 10 min. The reaction was stirred at 15 °C for 1 h and diluted with EtOAc (80 mL). The mixture was washed with *sat.* $Na_2S_2O_3$ (30 mL*2), *sat.* $NaHCO_3$ (30 mL*2) and brine (50 mL*2), dried over Na_2SO_4, filtered and concentrated. The residue was stirred in acetonitrile (5 mL) for 30 min and filtered. The filter cake was dried to afford **30c** (1.63 g, 41% yield) as a white solid. LC-MS (ESI, Method 3) t_R = 0.88 min, m/z $(M+H)^+$ = 346.1.

Step 4. *N'*-(4-methoxypyrazolo[1,5-*c*]pyrimidin-5-yl)-*N*,*N*-dimethylformimidamide (30d)

[00376] To a solution of **30c** (600 mg, 1.74 mmol) and TEA (352 mg, 3.48 mmol, 0.48 mL) in MeOH/THF (4 mL/4 mL) was added Pd/C (60 mg, 10% on carbon wetted with 50% water) and $Pd(OH)_2$/C (60 mg, 10% on carbon wetted with 55% water) at 10 °C. The mixture was stirred at 30 °C under H_2 (1 atm) for 24 h. The mixture was filtered and the filtrate was concentrated to afford **30d** (350 mg, 92% yield) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI, Method 3) t_R = 0.66 min, m/z $(M+H)^+$= 220.1.

Step 5. *N*'-(4-methoxy-3-(2,2,2-trifluoroacetyl)pyrazolo[1,5-*c*]pyrimidin-5-yl)-*N*,*N*-dimethylformimidamide (30e)

[00377] To a solution of **30d** (350 mg, 1.60 mmol) in pyridine (3 mL) was slowly added trifluoroacetic anhydride (503 mg, 2.39 mmol, 0.33 mL) at 0 °C. The reaction was stirred at 0 °C for 10 min and at 30 °C for 12 h. The reaction mixture was concentrated to dryness and purified by flash chromatography on silica gel (PE/EA = 1/1) to afford **30e** (150 mg, 30% yield) as a brown solid. LC-MS (ESI, Method 3) t_R = 0.97 min, m/z $(M+H)^+$ = 316.3.

Step 6. 1-(5-Amino-4-methoxypyrazolo[1,5-*c*]pyrimidin-3-yl)-2,2,2-trifluoroethan-1-one (30f)

[00378] To a solution of **30e** (150 mg, 0.48 mmol) in HCl/MeOH (0.5 M, 0.5 mL) was stirred at 80 °C for 1.5 h. The solution was basified with *sat.* Na_2CO_3 (3 mL) to pH > 9 and extracted with EtOAc (3 mL*3). The organic layer was concentrated and purified by *prep*-TLC (DCM/MeOH = 10/1) to get compound **30f** (35 mg, 28% yield) as a yellow solid. LC-MS (ESI, Method 3) t_R = 1.04 min, m/z $(M+H)^+$ = 261.0.

Step 7. 1-(5-Amino-4-methoxypyrazolo[1,5-*c*]pyrimidin-3-yl)-2,2,2-trifluoroethan-1-ol (30g)

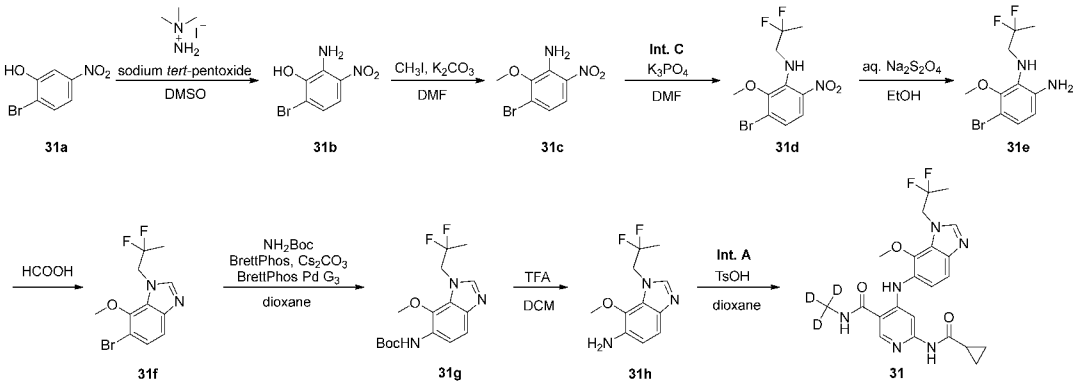
[00379] To a solution of **30f** (35 mg, 0.13 mmol) in MeOH (1 mL) was added $NaBH_4$ (11 mg, 0.27 mmol) at -5 °C. After stirred at -5 °C for 0.5 h, the mixture was diluted with water (1 mL) and extracted with EtOAc (3 mL). The organic layer was washed with brine (1 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated to afford **30g** (30 mg, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.98 (s, 1H), 5.39-5.37 (m, 1H), 4.49 (s, 2H), 3.91 (s, 3H), 3.43-3.41 (m, 1H). LC-MS (ESI, Method 3) t_R = 0.92 min, m/z $(M+H)^+$ = 263.0.

Step 8. 6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-*c*]pyrimidin-5-yl)amino)-*N*-(methyl-d_3)nicotinamide (30)

[00380] A mixture of **30g** (10 mg, 0.038 mmol), **Int. A** (10 mg, 0.038 mmol), dppf (8 mg, 0.015 mmol), $Pd(OAc)_2$ (2 mg, 0.0076 mmol), K_3PO_4 (24 mg, 0.114 mmol) in dioxane (0.5 mL) was stirred at 100 °C for 16 h. The mixture was concentrated and purified by *prep*-HPLC (Method E) to get compound **30** (10 mg, 54% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.80 (s, 1H), 9.37 (s, 1H), 8.96 (s, 1H), 8.72 (s, 1H), 8.59 (s, 1H), 8.20 (s, 1H), 6.89 (d, J = 6.0 Hz, 1H), 5.50-5.43 (m, 1H), 3.89 (s, 3H), 2.02-1.97 (m, 1H), 0.81-

0.79 (m, 4H). LC-MS (ESI, Method 4) t_R = 1.98 min, m/z $(M+H)^+$ = 483.3.

Example 31



Step 1. 2-Amino-6-bromo-3-nitro-phenol (31b)

[00381] To a solution of **31a** (4.50 g, 20.64 mmol) in DMSO (60 mL) was added 1,1,1-trimethylhydrazinium iodide (4.59 g, 22.71 mmol). The mixture was stirred at r.t. for 90 min, then sodium *tert*-pentoxide (11.37 g, 103.21 mmol) was added. The resulting mixture was further stirred at r.t. for 2 h. Aq. HCl (62 mL, 2 M) was added at 0 °C and the mixture was stirred for 1 h. The mixture was diluted with H_2O (100 mL), extracted with EtOAc (50 mL*3), washed with brine (100 mL), dried over Na_2SO_4 and concentrated to get compound **31b** (4.76 g, 98% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (brs, 1H),7.49 (d, J = 9.6 Hz, 1H), 7.18 (brs, 2H), 6.76 (d, J = 9.6 Hz, 1H). LC-MS (ESI, Method 4) t_R = 2.29 min, m/z (^{79}Br, $M+H)^+$ = 233.0.

Step 2. 3-Bromo-2-methoxy-6-nitro-aniline (31c)

[00382] A mixture of **31b** (4.76 g, 20.43 mmol), K_2CO_3 (6.21 g, 44.94 mmol) and iodomethane (3.19 g, 22.47 mmol, 1.40 mL) in DMF (50 mL) was stirred at 20 °C for 2 h. A brown suspension was formed. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (100 mL*3). The combined organic layer was washed with water (100 mL*3) and brine (100 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (EtOAc in PE is 10-60%) to give **31c** (3.10 g, 61% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 2.86 min, m/z (^{79}Br, $M+H)^+$ = 247.0.

Step 3. 3-Bromo-*N*-(2,2-difluoropropyl)-2-methoxy-6-nitro-aniline (31d)

[00383] To a solution of **31c** (300 mg, 1.21 mmol) in DMF (5 mL) was added K_3PO_4 (516

mg, 2.43 mmol) and Int. **C** (489 mg, 1.82 mmol). The resulting mxiture was stirred at 30 °C for 48 h. The mixture was diluted with H_2O (50 mL), extracted with EtOAc (50 mL*3), washed with water (50 mL*3) and brine (50 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (EtOAc in PE is 5-20%) to give **31d** (200 mg, 51% yield) as a yellow oil. LC-MS (ESI, Method 4) t_R = 3.40 min, m/z (^{79}Br, M+H)$^+$ = 325.0.

Step 4. 5-Bromo-*N*^{1}-(2,2-difluoropropyl)-6-methoxybenzene-1,2-diamine (31e)

[00384] To a solution of **31d** (200 mg, 0.61 mmol) in EtOH (5 mL) was added aq. $Na_2S_2O_4$ (5.0 mL, 1 M). The resulting mixture was stirred at 80 °C for 2 h. 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) and brine (50 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated to give **31e** (180 mg, crude) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI, Method 4) t_R = 2.96 min, m/z (^{79}Br, M+H)$^+$ = 295.1.

Step 5. 6-Bromo-1-(2,2-difluoropropyl)-7-methoxy-benzimidazole (31f)

[00385] A mixture of **31e** (180 mg, 0.61 mmol) in HCOOH (1 mL) was stirred at 100 °C for 2 h. The reaction mixture was concentrated in vacuo and diluted with aq. $NaHCO_3$ (50 mL), then extracted with EtOAc (50 mL*2). The combined organic layer was washed with water (50 mL*2) and brine (50 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) to give **31f** (100 mg, 54% yield for 2 steps) as a light yellow solid. LC-MS (ESI, Method 4) t_R = 2.64 min, m/z (^{79}Br, M+H)$^+$ = 305.1.

Step 6. *Tert*-butyl (1-(2,2-difluoropropyl)-7-methoxy-1*H*-benzo[*d*]imidazol-6-yl)carbamate (31g)

[00386] A mixture of **31f** (90 mg, 0.29 mmol), *tert*-butyl carbamate (52 mg, 0.44 mmol), BrettPhos Pd G3 (27 mg, 0.03 mmol), BrettPhos (32 mg, 0.59 mmol), K_3PO_4 (313 mg, 1.47 mmol) in dioxane (3 mL) was stirred at 100 °C for 16 h under N_2. The reaction mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by

flash chromatography (MeOH in DCM is 0-8%) to give **31g** (100 mg, 99% yield) as a yellow soild. LC-MS (ESI, Method 4) t_R = 2.45 min, m/z $(M+H)^+$ = 342.2.

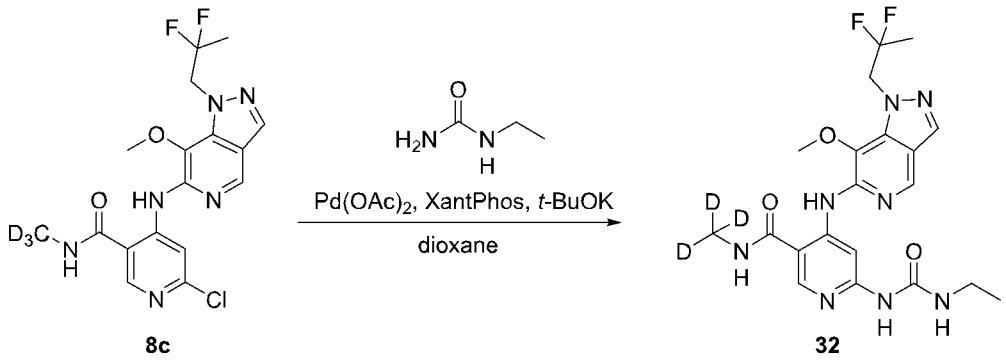
Step 7. 3-(2,2-Difluoropropyl)-4-methoxy-benzimidazol-5-amine (31h)

[00387] To a solution of **31g** (100 mg, 0.29 mmol) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at r.t. for 1 h. The mixture was concentrated and quenched with *sat.* $NaHCO_3$ (40 mL), then extracted with EtOAc (20 mL*3). The organic layer was washed with aq. $NaHCO_3$ (30 mL) and brine (30 mL). The separated solution was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) to give **31h** (60 mg, 85% yield) as a yellow solid. LC-MS (ESI, Method 4) t_R = 0.51 min, m/z (ESI, $M+H)^+$ = 242.0.

Step 8. 6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1*H*-benzo[*d*]imidazol-6-yl)amino)-*N*-(methyl-d_3)nicotinamide (31)

[00388] A mixture of **31h** (60 mg, 0.25 mmol), **Int. A** (58 mg, 0.22 mmol), pTSA (58 mg, 0.34 mmol) in dioxane (3 mL) was stirred at 100 °C for 24 h. The reaction mixture was concentrated in vacuo and diluted with aq. $NaHCO_3$ (30 mL), then extracted with EtOAc (30 mL*2). The combined organic layer was washed with water (50 mL*2) and brine (50 mL*2), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (MeOH in DCM is 0-10%) to give a yellow solid, which was further purified by *prep*-HPLC (Method D) to get **31** (30.0 mg, 26% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 10.37 (s, 1H), 8.58 (s, 1H), 8.50 (s, 1H), 8.14 (s, 1H), 7.67 (s, 1 H), 7.44 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.87 (t, J = 14.4 Hz, 2H), 3.75 (s, 3H), 1.96-1.89 (m, 1H), 1.68 (t, J = 19.2 Hz, 3H), 0.74-0.66 (m, 4H). LC-MS (ESI, Method 4) t_R = 1.71 min, m/z $(M+H)^+$ = 462.4.

Example 32

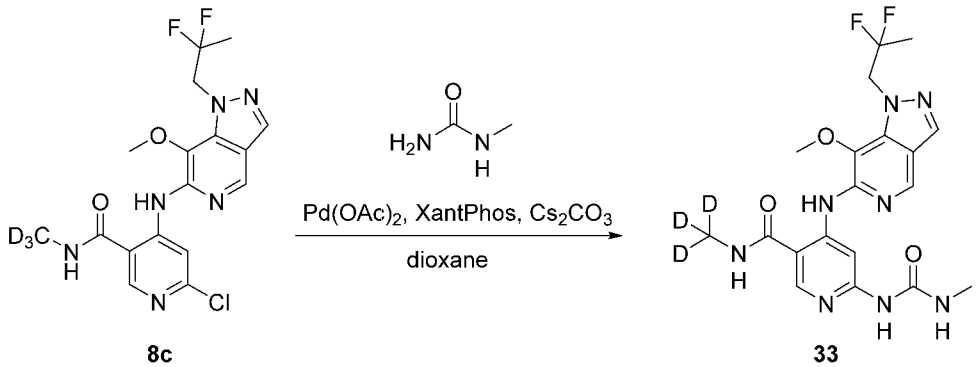


8c 32

Step 1. 4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-6-(3-ethylureido)-*N*-(methyl-d_3)nicotinamide (32)

[00389] To a solution of **8c** (10 mg, 0.024 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), XantPhos (6 mg, 0.01 mmol), *t*-BuOK (8 mg, 0.072 mmol) in dioxane (3 mL) was added 1-ethylurea (11 mg, 0.12 mmol) at r.t.. The reaction was stirred at 100 °C for 5 h under nitrogen protection. The resulting solution was added into H_2O (10 mL) and extracted by EA (20 mL). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude was purified by *prep*-HPLC (Method E) to afford **32** (4 mg, 35% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 9.26 (s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.50 (s, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 8.31-8.25 (m, 1H), 4.93 (t, J = 13.2 Hz, 2H), 3.90 (s, 3H), 3.24-3.13 (m, 2H), 1.70 (t, J = 19.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 2.04 min, m/z $(M+H)^+$ = 466.4.

Example 33

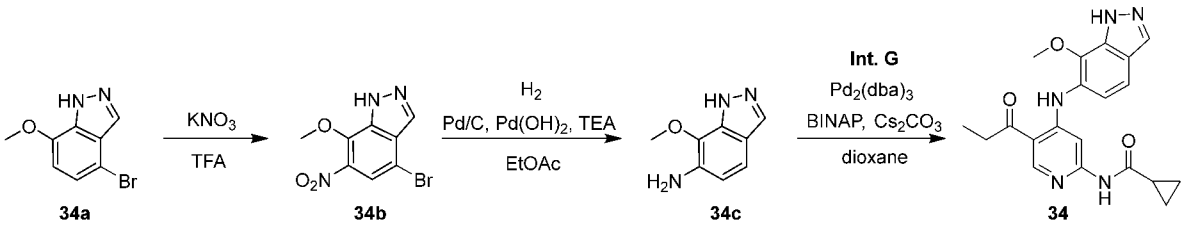


8c 33

4-((1-(2,2-Difluoropropyl)-7-methoxy-1*H*-pyrazolo[4,3-*c*]pyridin-6-yl)amino)-*N*-(methyl-*d*3)-6-(3-methylureido)nicotinamide (33)

[00390] To a solution of **8c** (20 mg, 0.048 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), XantPhos (11 mg, 0.02 mmol) in dioxane (3 mL) was added 1-methylurea (18 mg, 0.24 mmol) at r.t.. The reaction was stirred at 100 °C for 5 h under nitrogen protection. The resulting solution was added into H_2O (10 mL) and extracted by EA (20 mL). The combined organic layer was washed by brine (10 mL*2), dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The crude was purified by p*rep*-HPLC (Method E) to afford **33** (1.2 mg, 6% yield) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.62 (s, 1H), 9.33 (s, 1H), 8.69 (s, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 8.35 (s, 1H), 8.25-8.16 (m, 1H), 4.93 (t, J = 12.8 Hz, 2H), 3.90 (s, 3H), 2.73 (d, J = 4.4 Hz, 3H), 1.70 (t, J = 19.2 Hz, 3H). LC-MS (ESI, Method 4) t_R = 1.88 min, m/z $(M+H)^+$ = 452.3.

Example 34



Step 1. 4-Bromo-7-methoxy-6-nitro-1*H*-indazole (34b)

[00391] To a solution of **34a** (400 mg, 1.76 mmol) in TFA (10 mL) was added KNO_3 (178 mg, 1.76 mmol) at r.t. The mixture was stirred at 70 °C for 1 h. After cooling to r.t., TFA was removed by pumping through N_2. The residue was dissolved in DCM (30 mL) and basified with *sat.* Na_2CO_3 to pH = 9. The mixture was extracted with EtOAc (200 mL*3). The combined organic phase was concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to afford **34b** (450 mg, 94% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.46 (s, 1H), 8.28 (s, 1H), 7.82 (s, 1H), 3.95 (s, 3H).

Step 2. 7-Methoxy-1*H*-indazol-6-amine (34c)

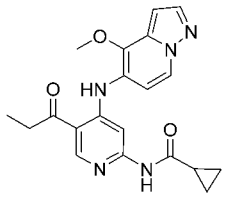
[00392] A mixture of **34b** (450 mg, 1.65 mmol), Pd/C (100 mg, palladium 10% on carbon wetted with 50% water), $Pd(OH)_2$ (100 mg, palladium hydroxide 10% on carbon wetted with ca. 55% water) and TEA (167 mg, 1.65 mmol, 0.23 mL) in EtOAc (8 mL) and MeOH (2 mL) was stirred at 30 °C for 3 h under H_2 (1 atom) atmosphere. The mixture was filtered and the filtrate was concentrated to afford **33c** (270 mg, yield given) as a brown solid. LC-MS (ESI, Method 3)

t_R = 0.72 min, m/z $(M+H)^+$ = 164.3.

Step 3. *N*-(4-((7-methoxy-1*H*-indazol-6-yl)amino)-5-propionylpyridin-2-yl)cyclopropanecarboxamide (34)

[00393] A mixture of **Int. G** (30 mg, 0.12 mmol), **34c** (58 mg, 0.14 mmol), $Pd_2(dba)_3$ (9 mg, 0.009 mmol), BINAP (8 mg, 0.011 mmol) and Cs_2CO_3 (77 mg, 0.24 mmol) in dioxane (1 mL) was stirred at 115 °C for 16 h under N_2 atmosphere. The reaction mixture was concentrated and the residue was purified by *prep*-TLC (DCM/MeOH = 20/1) to afford **34** (10 mg, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.39 (s, 1H), 10.90 (s, 1H), 10.85 (s, 1H), 8.85 (s, 1H), 8.11 (s, 1H), 7.70 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.12 (q, J = 7.2 Hz, 2H), 1.99-1.95 (m, 1H), 1.13 (t, J = 7.2 Hz, 3H), 0.76-0.72 (m, 4H). LC-MS (ESI, Method 2) t_R = 1.10 min, m/z $(M+H)^+$ = 380.0.

Example 35

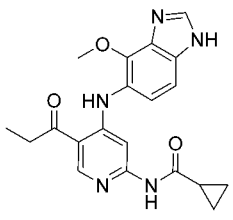


35

***N*-[4-[(4-methoxypyrazolo[1,5-*a*]pyridin-5-yl)amino]-5-propanoyl-2-pyridyl]cyclopropanecarboxamide (35)**

[00394] The synthesis of compound **35** refers to the patent (CN115466257A, page 24-26). LC-MS (ESI, Method 4) t_R = 0.72 min, m/z $(M+H)^+$ = 380.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.02 (brs, 1H), 8.71 (s, 1H), 8.42 (brs, 1H), 8.29 (d, J = 7.2 Hz, 1H), 7.93 (s, 1H), 7.90 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H), 4.00 (s, 3H), 3.03 (q, J = 7.2 Hz, 2H), 1.58-1.49 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.09-1.03 (m, 2H), 0.92-0.85 (m, 2H).

Example 36

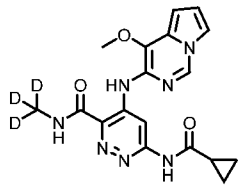


36

***N*-[4-[(4-methoxy-1*H*-benzimidazol-5-yl)amino]-5-propanoyl-2-pyridyl] cyclopropanecarboxamide (36)**

[00395] The synthesis of compound **36** refers to the patent (CN115466257A, page 33-34). LC-MS (ESI, Method 4) t_R = 0.52 min, m/z $(M+H)^+$ = 380.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.98 (s, 1H), 9.82 (brs, 1H), 8.61 (s, 1H), 8.61 (s, 1H), 7.94 (s, 1H), 7.70 (s, 1H), 7.23-7.13 (m, 2H), 4.28 (s, 3H), 3.03 (q, J = 7.2 Hz, 2H), 1.72-1.62 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.03-0.95 (m, 2H), 0.91-0.82 (m, 2H).

Example 37



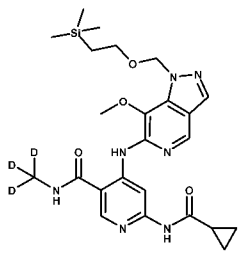
38

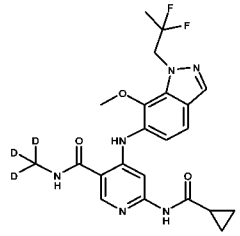
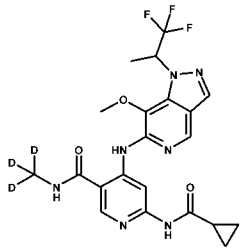
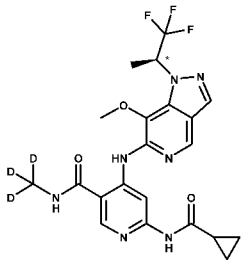
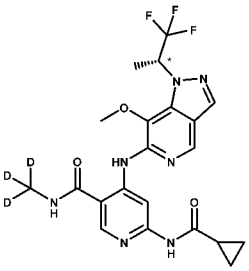
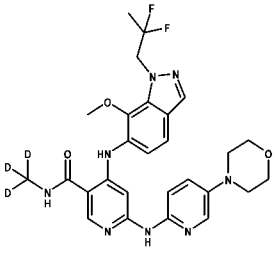
6-(cyclopropanecarboxamido)-4-((4-methoxypyrrolo[1,2-*c*]pyrimidin-3-yl)amino)-*N*-(methyl-d_3)pyridazine-3-carboxamide (37)

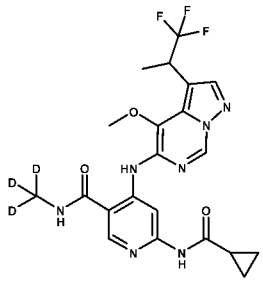
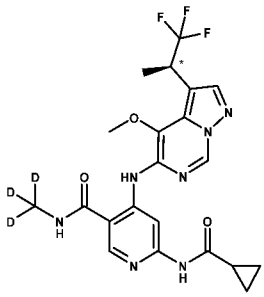
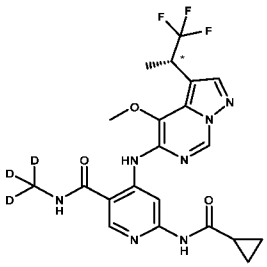
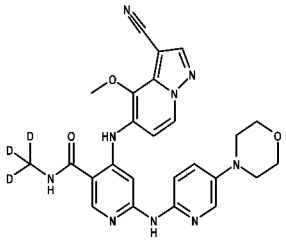
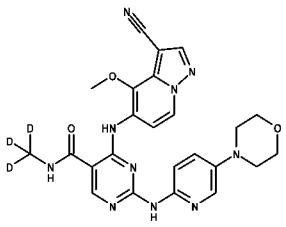
[00396] The synthesis of compound **37** refers to the patent (CN116262739A, page 35-36). LC-MS (ESI, Method 4) t_R = 0.76 min, m/z $(M+H)^+$ = 385.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50 (s, 1H), 11.24 (s, 1H), 9.14 (s, 1H), 9.01 (s, 1H), 8.99 (d, J = 0.8 Hz, 1H), 7.67 (dd, J = 2.8, 1.2 Hz, 1H), 6.90 (dd, J = 3.6, 2.8 Hz, 1H), 6.56-6.53 (m, 1H), 3.99 (s, 3H), 2.13-2.07 (m, 1H), 0.84 (d, J = 6.4 Hz, 4H).

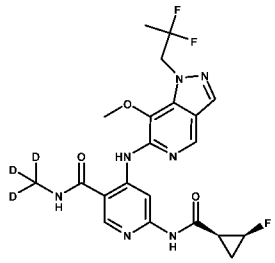
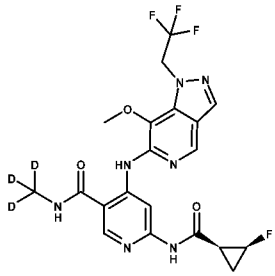
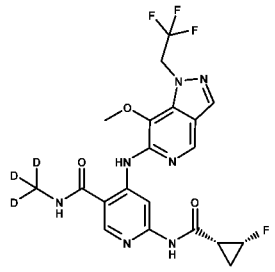
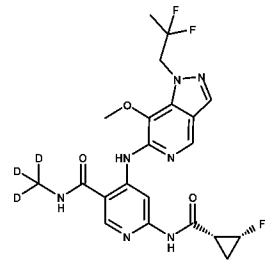
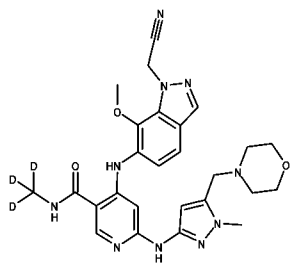
[00397] A Summary of representative compounds are shown in **Table 1A**.

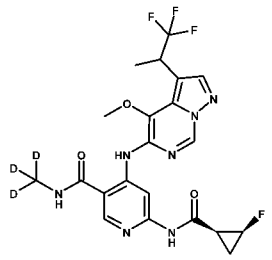
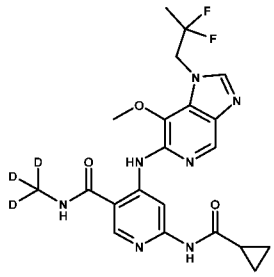
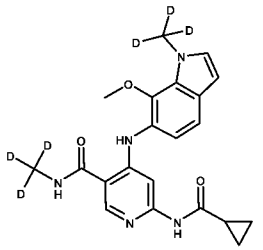
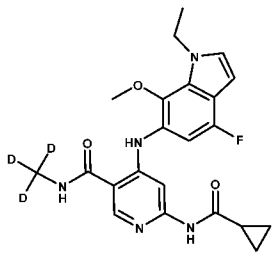
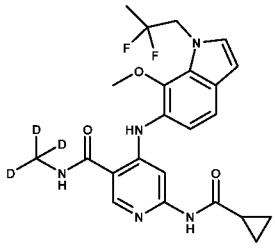
Table 1A. Exemplary Compounds

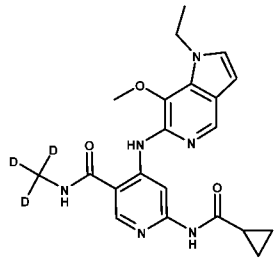
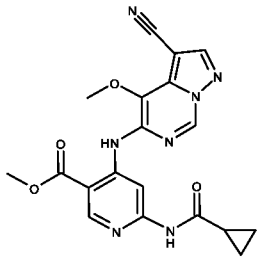
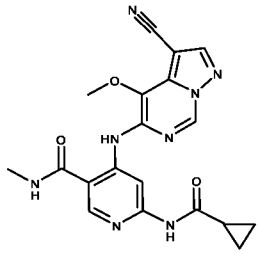
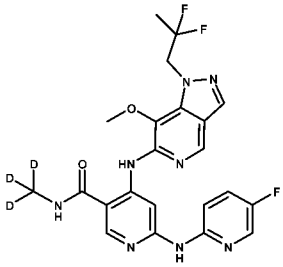
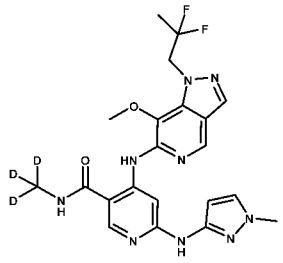
Example	Structure	Name	Mol Weight
1		6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	514.67

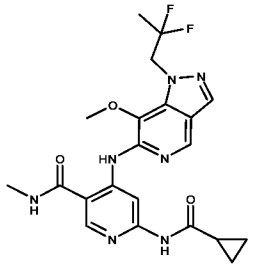
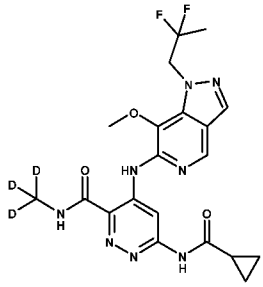
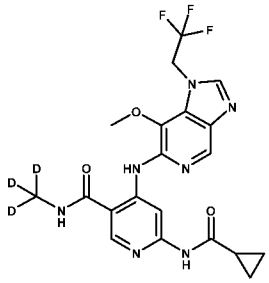
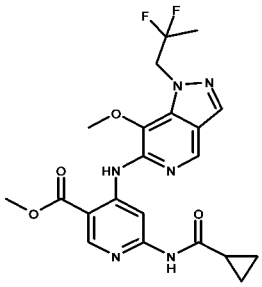
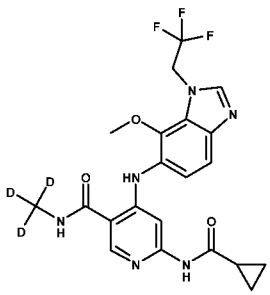
2		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-indazol-6-yl)amino)-N-(methyl-d3)nicotinamide	461.48
3		6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	480.46
3A		(R*)-6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	480.46
3B		(S*)-6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	480.46
4		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-indazol-6-yl)amino)-N-(methyl-d3)-6-((5-morpholinopyridin-2-yl)amino)nicotinamide	555.59

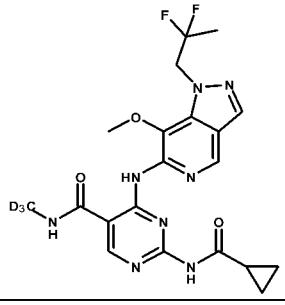
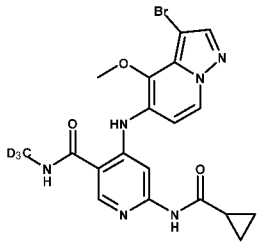
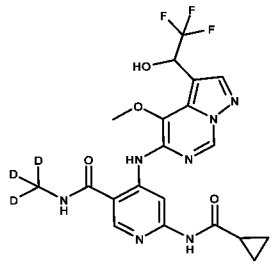
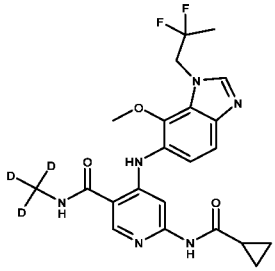
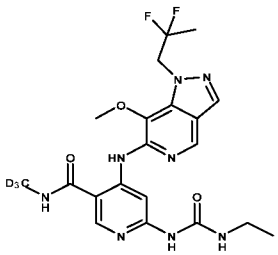
5		6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide	480.46
5A		(R*)6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide	480.46
5B		(S*)6-(Cyclopropanecarboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide	480.46
6		4-((3-Cyano-4-methoxypyrazolo[1,5-a]pyridin-5-yl)amino)-N-(methyl-d3)-6-((5-morpholinopyridin-2-yl)amino)nicotinamide	502.54
7		4-((3-Cyano-4-methoxypyrazolo[1,5-a]pyridin-5-yl)amino)-N-(methyl-d3)-2-((5-morpholinopyridin-2-yl)amino)pyrimidine-5-carboxamide	503.53

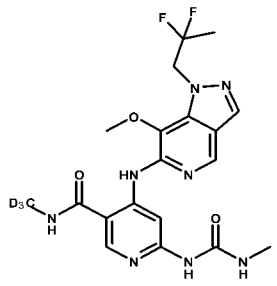
8		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d3)nicotinamide	480.46
9		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	484.42
10		6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	484.42
11		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-6-((1R,2R)-2-fluorocyclopropane-1-carboxamido)-N-(methyl-d3)nicotinamide	480.46
12		4-((1-(Cyanomethyl)-7-methoxy-1H-indazol-6-yl)amino)-N-(methyl-d3)-6-((1-methyl-5-(morpholinomethyl)-1H-pyrazol-3-yl)amino)nicotinamide	533.60

13		6-((1S,2S)-2-fluorocyclopropane-1-carboxamido)-4-((4-methoxy-3-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide	498.45
14		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-imidazo[4,5-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	462.47
15		6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(methyl-d3)-1H -indol-6-yl)amino)-N-(methyl-d3)nicotinamide	399.48
16		6-(Cyclopropanecarboxamido)-4-((1-ethyl-4-fluoro-7-methoxy-1H-indol-6-yl)amino)-N-(methyl-d3)nicotinamide	428.47
17		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-indol-6-yl)amino)-N-(methyl-d3)nicotinamide	460.49

18		6-(Cyclopropanecarboxamido)-4-((1-ethyl-7-methoxy-1H-pyrrolo[3,2-c] pyridin-6-yl) amino)-N-(methyl-d3)nicotinamide	411.47
19		Methyl 4-((3-cyano-4-methoxypyrazolo[1,5-c]pyrimidin-5-yl)amino)-6-(cyclopropanecarboxamido)nicotinate	407.38
20		4-((3-Cyano-4-methoxypyrazolo[1,5-c]pyrimidin-5-yl)amino)-6-(cyclopropanecarboxamido)-N-methylnicotinamide	406.40
21		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-6-((5-fluoropyridin-2-yl)amino)-N-(methyl-d3)nicotinamide	489.47
22		4-((1-(2,2-Difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)-6-((1-methyl-1H-pyrazol-3-yl)amino)nicotinamide	474.48

23		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-methylnicotinamide	459.45
24		6-(Cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)pyridazine-3-carboxamide	463.46
25		6-(Cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1H-imidazo[4,5-c]pyridin-6-yl)amino)-N-(methyl-d3)nicotinamide	466.43
26		Methyl 6-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)nicotinate	460.43
27		6-(cyclopropanecarboxamido)-4-((7-methoxy-1-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazol-6-yl)amino)-N-(methyl-d3)nicotinamide	465.44

28		2-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)pyrimidine-5-carboxamide	463.46
29		4-((3-bromo-4-methoxypyrazolo[1,5-a]pyridin-5-yl)amino)-6-(cyclopropanecarboxamido)-N-(methyl-d3)nicotinamide	462.31
30		6-(cyclopropanecarboxamido)-4-((4-methoxy-3-(2,2,2-trifluoro-1-hydroxyethyl)pyrazolo[1,5-c]pyrimidin-5-yl)amino)-N-(methyl-d3)nicotinamide	482.43
31		6-(cyclopropanecarboxamido)-4-((1-(2,2-difluoropropyl)-7-methoxy-1H-benzo[d]imidazol-6-yl)amino)-N-(methyl-d3)nicotinamide	461.48
32		4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-6-(3-ethylureido)-N-(methyl-d3)nicotinamide	465.48

33		4-((1-(2,2-difluoropropyl)-7-methoxy-1H-pyrazolo[4,3-c]pyridin-6-yl)amino)-N-(methyl-d3)-6-(3-methylureido)nicotinamide	451.45

Note: A asterisk * at the chiral center in the chemical structures or the S* or R* in the names means the compound is a chiral pure but absolute configuration unknown single isomer.

Binding Activity test for JH2 domain of JAK1 and TYK2

[00398] 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.

[00399] 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 wells 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

[00400] 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 IC50(nM)	JAK1 JH2 Binding IC50(nM)	JAK1/TYK2 selectivity
1	9.309	>298.5	>32.07
2	0.239	18.873	78.97
3	0.682	121.087	177.55
3A	8.544	>298.5	>34.94
3B	0.805	113.795	141.36
4	0.165	8.453	51.23
5	0.271	160.049	590.59
5A	1.511	>298.5	>197.55
5B	0.197	141.061	716.05
6	0.157	0.703	4.48
7	0.404	10.746	26.60
8	0.288	161.874	561.99
9	0.212	35.209	166.08
10	0.408	35.105	86.04
11	0.325	73.828	227.16
12	0.189	1.616	8.55
13	1.702	>298.5	>175.38
14	0.178	38.779	217.86
15	0.094	1.47	15.64

16	0.083	5.818	70.10
17	0.341	41.464	121.60
18	0.049	4.094	83.55
19	1.634	22.069	13.51
20	0.304	19.339	63.62
21	0.396	139.817	353.07
22	2.623	297.209	113.31
23	0.315	125.589	398.70
24	0.271	21.643	79.86
25	0.174	46.721	268.51
26	0.26	115.263	443.32
27	2.768	>298.5	>107.8
28	>298.5	>298.5	/
29	0.188	7.870	42.0
30	0.134	110.154	822.4
31	0.300	20.772	69.3
32	1.702	>298.5	>175.4
33	2.136	>298.5	>139.8
34	3.940	31.670	8.0
BMS986165	0.133	0.631	4.7
35	2.96	67.124	22.68
36	2.716	17.402	6.41

37	1.48	10.36	7.0

BMS986165, See, PCT/CN2022/139649 (filed on December 16, 2022), Example 41.

[00401] Exemplary compounds showed good selectivity over JAK1. These compounds can be used to eliminate the side effects caused by JAK1 inhibition in autoimmune disease.

Biochemical assay

Testing for JAK1, JAK2 and TYK2 Kinase Activities

[00402] JAK activity was determined in the reaction buffer 50 mM HEPES, 0.01% Brij35, 10 mM $MgCl_2$, 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.

[00403] The test compounds were dissolved in DMSO to a stock concentration of 10 mM. Three-fold serially diluted compounds with top concentration of 5 μM 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 μM) 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.

[00404] 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:

$$\%\ \text{Inhibition} = \frac{\text{Conversion\%\_max} - \text{Conversion\%\_sample}}{\text{Conversion\%\_max} - \text{Conversion\%\_min}} \times 100$$

wherein

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

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

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

[00405] 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
4	>20000	>20000	>20000
23	>20000	>20000	>20000
24	>20000	>20000	>20000
276*	>20000	>20000	>20000

Example 276*: See, PCT/CN2022/139649 (filed on December 16, 2022), Example 276.

[00406] Exemplary compounds showed excellent selectivity over JAK1, JAK2 and TYK2 kinase domain inhibition.

Anti-proliferative assay

[00407] 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 μM was added into the each well. The final DMSO concentration was 0.1%. The cells continued to grow at 37℃ in 5% CO_2 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:

$$\%\ \text{Inhibition} = 100 - \frac{\text{RLU\_compound} - \text{RLU\_blank}}{\text{RLU\_control} - \text{RLU\_blank}} \times 100\%$$

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

[00408] 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	442.3	**16**	16.55
2	86.9	**17**	58.06
3	164.2	**18**	3.69
3A	1804	**19**	233.4
3B	164.15	**20**	62.34
4	22.07	**21**	63.09
5	52.36	**22**	329.8
5A	>5000.0	**23**	78.43
5B	62.26	**24**	54.82
6	231	**25**	99
7	147.22	**26**	726.4
8	72.69	**27**	128.0
9	66.75	**28**	>5000.0
10	117.85	**29**	39.51
11	160	**30**	62.86
12	54.6	**31**	135.20
13	499.3	**32**	/

14	145.5	**33**	/
15	20.99	**34**	856.90

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

[00409] *Purpose:* To evaluate the inhibition activity of TYK2 inhibitors in NK92 cells on TYK2 pathway through ELISA method.

[00410] *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™ 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

[00411] *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 CO_2 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	IC50 on TYK2 pathway (nM)
262*	26.27
266*	37.9
276*	27.7
4	14.01
17	21.73
23	17.45
24	8.94
29	32.09
34	922.8
35	1500
36	515.1

Example 262*, 266* and 276*: See, PCT/CN2022/139649 (filed on 16 December 2022, incorporated herein by reference), Example 262,266 and 276, respectively.

[00412] Exemplary compounds showed good TYK2 pathway inhibition activity in cells.

Phosphorylation Inhibition of STAT in Human Whole Blood Testing:

[00413] The inhibitory potential of test articles in human whole blood assay was evaluated by the method of flow cytometry.

[00414] IFN-alpha 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-gamma. To evaluate the efficacy of TYK2i in T cells, freshly collected human whole blood will be stimulated with certain unit of human IFN-alpha (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.

[00415] Exemplary results are summarized in **Table 6**.

Table 6

Example	pSTAT1 inhibition in hWB (IC50, nM)	Example	pSTAT1 inhibition in hWB (IC50, nM)
2	327.4	**20**	166.8
4	151.6	**276***	176.6
9	273.6	**34**	>10000
15	204.9	**35**	>5000
16	219.7	**37**	1469

ADME

Microsomal Metabolic Stability assay

[00416] 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.

[00417] 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).

[00418] In the determination of the in vitro elimination constant （ke） of the control compounds, the analyte/internal standard peak area ratios will be converted to percentage remaining (%Remaining) with the following equation:

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

[00419] The CL_{int} of microsomes was calculated using the formula: $CL_{int\ (mic)}=0.693/T_{1/2}$ /mg microsome protein per mL. The slope was measured by the natural logarithm of the percentage of the residual compound and time, T1/2 was calculated according to the following formula.

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

[00420] Exemplary results are summarized in **Table 7**.

Table 7

Example	Human LM T1/2 (min)	Human LM Clint (uL/min/mg)
2	25.77	53.79
3	239.11	5.80
3A	223.67	6.20
3B	259.98	5.33
5	27.69	50.06
5A	24.08	57.55
5B	29.11	47.61
6	48.84	28.38
7	49.33	28.10
9	255.94	5.42
10	308.79	4.49
11	485.14	2.86
13	54.49	25.44

14	35.33	39.23
20	35.36	39.20
21	84.8	16.34
22	149.78	9.25
24	333.09	4.16
34	2.89	479.76
276*	290.03	6.12

Kinetic solubility

[00421] Aliquots of 8 μL of reference and test compound stock solutions (10 mM/5 mM) are added into 792 μL 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 μL of samples (no diluted, 10 times diluted and 100 times diluted) and standard curve samples to 95 μL of ACN containing IS for LC-MS/MS analysis.
Exemplary results are summarized in **Table 8**

Table 8

Example	Kinetics Solubility_PBS7.4(μM)
3A	19.05
3B	12.75
4	61.75
9	38.2
10	29
12	7.21
14	16.9
17	11.11
18	41.49
22	19.8
27	44.25
28	20.6
276*	12.79

[00422] Exemplary compounds showed ideal solubility for further development.

[00423] 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.

[00424] 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.

[00425] 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

[00426] 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.

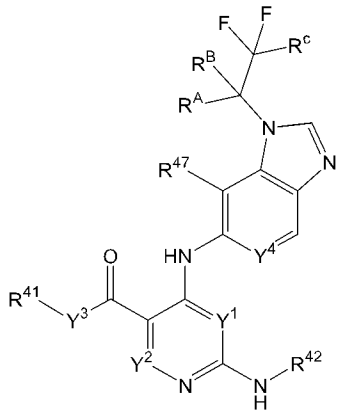
Equivalents

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):



(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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

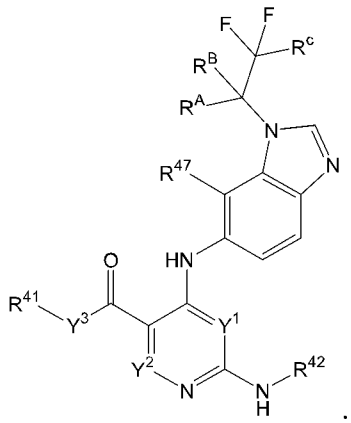
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

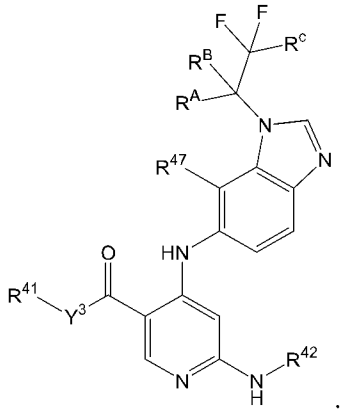
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

2. The compound of claim 1, wherein Y^4 is CH, having the structure:



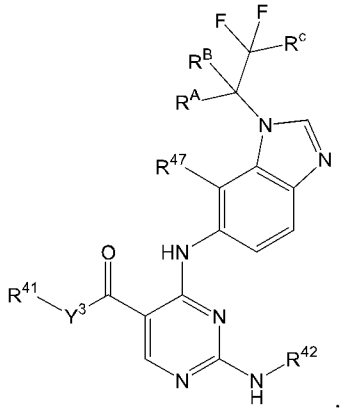
(I^a)

3. The compound of claim 2, wherein Y^1 is CH and Y^2 is CH, having the structure:



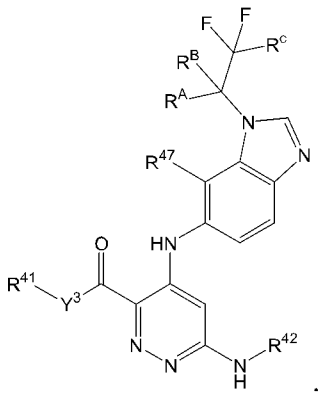
(I^b)

4. The compound of claim 2, wherein Y^1 is N and Y^2 is CH, having the structure:



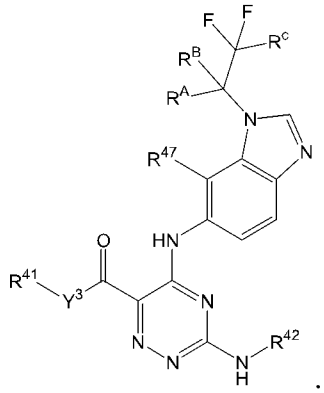
(I^c)

5. The compound of claim 2, wherein Y^1 is CH and Y^2 is N, having the structure:



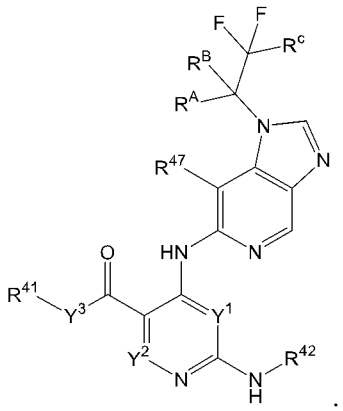
(I^6)

6. The compound of claim 2, wherein Y^1 is N and Y^2 is N, having the structure:



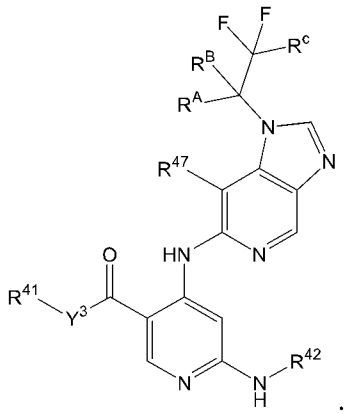
(I^e)

7. The compound of claim 1, wherein Y^4 is N, having the structure:



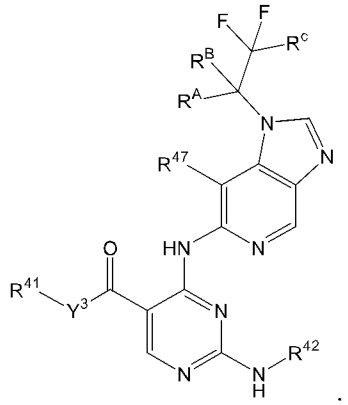
(I^f)

8. The compound of claim 7, wherein Y^1 is CH and Y^2 is CH, having the structure:



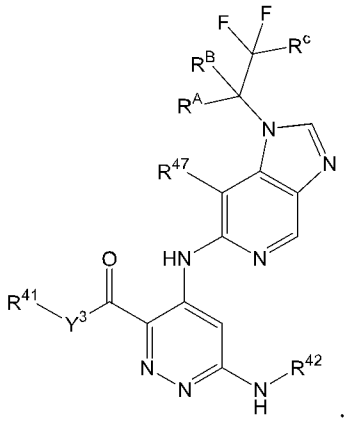
(I^g)

9. The compound of claim 7, wherein Y^1 is N and Y^2 is CH, having the structure:



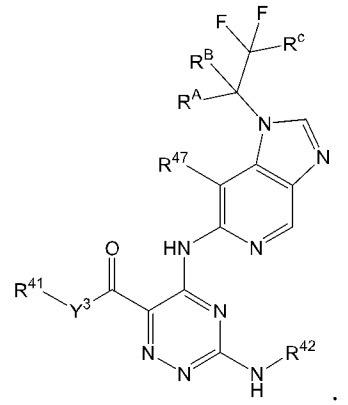
(I^h)

10. The compound of claim 7, wherein Y^1 is CH and Y^2 is N, having the structure:



(I^i)

11. The compound of claim 7, wherein Y^1 is N and Y^2 is N, having the structure:



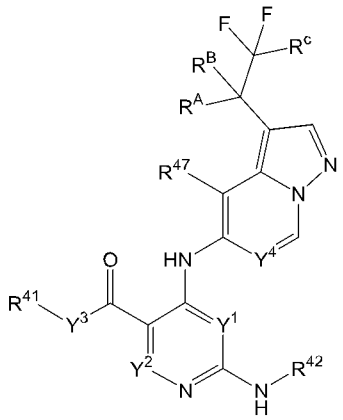
(I^j)

12. The compound of any one of claims 1-11, wherein R^A is H and R^B is H.

13. The compound of any one of claims 1-12, wherein R^C is CH_3.

14. The compound of any one of claims 1-12, wherein R^C is not CH_3.

15. A compound having the structural formula (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

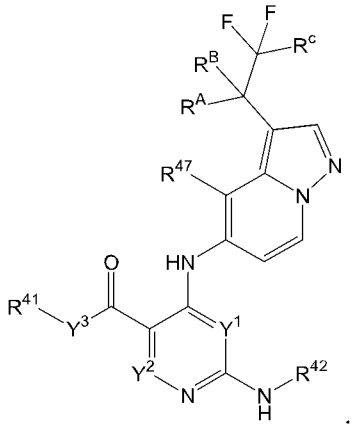
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

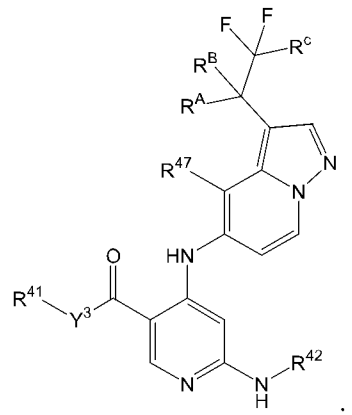
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

16. The compound of claim 15, wherein Y^4 is CH, having the structure:



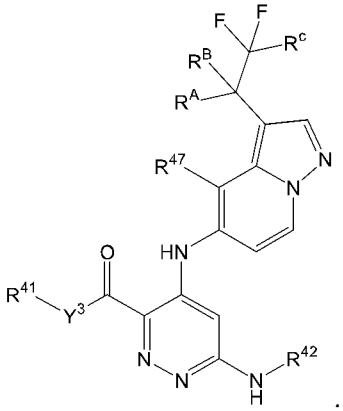
(II^a)

17. The compound of claim 16, wherein Y^1 is CH and Y^2 is CH, having the structure:



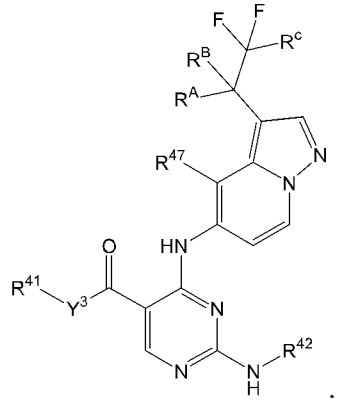
(II^b)

18. The compound of claim 16, wherein Y^1 is CH and Y^2 is N, having the structure:



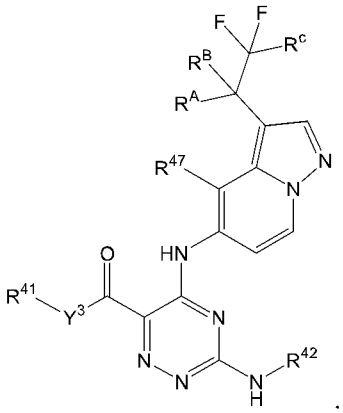
(II^c)

19. The compound of claim 16, wherein Y^1 is N and Y^2 is CH, having the structure:



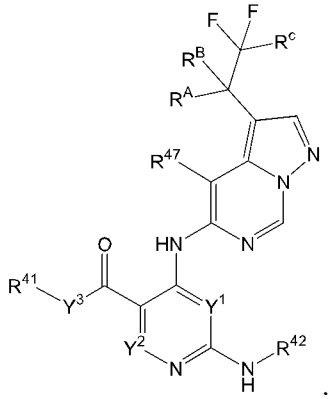
(II^d)

20. The compound of claim 16, wherein Y^1 is N and Y^2 is N, having the structure:



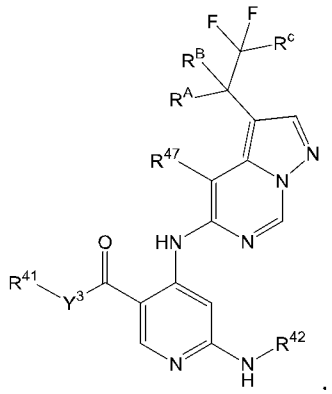
(II^e)

21. The compound of claim 15, wherein Y^4 is N, having the structure:



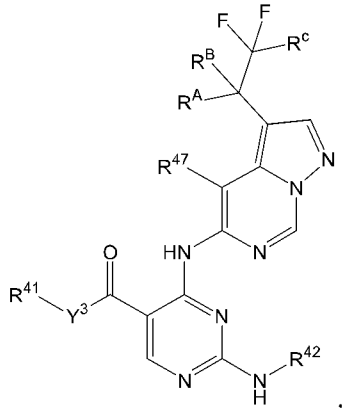
(II^f)

22. The compound of claim 21, wherein Y^1 is CH and Y^2 is CH, having the structure:



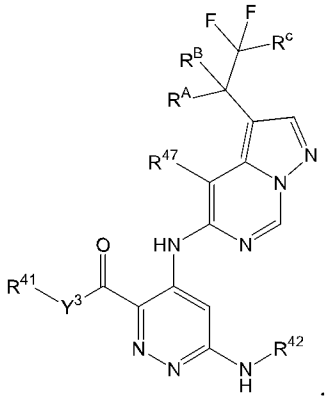
(II^g)

23. The compound of claim 21, wherein Y^1 is N and Y^2 is CH, having the structure:



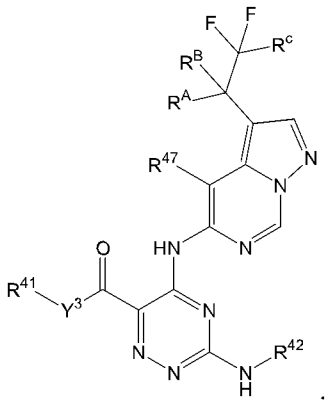
(II^h)

24. The compound of claim 21, wherein Y^1 is CH and Y^2 is N, having the structure:



(II^{i})

25. The compound of claim 21, wherein Y^1 is N and Y^2 is N, having the structure:



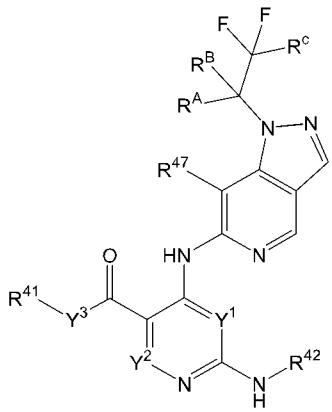
(II^{j})

26. The compound of any one of claims 15-25, wherein R^A is H and R^B is H.

27. The compound of any one of claims 15-26, wherein R^C is CH_3.

28. The compound of any one of claims 15-26, wherein R^C is not CH_3.

29. A compound having the structural formula (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

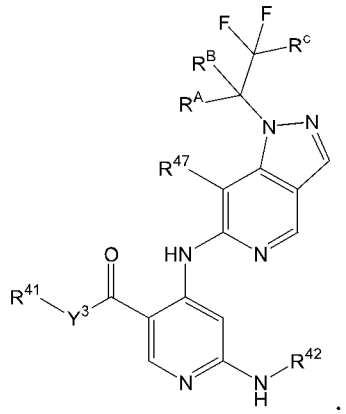
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

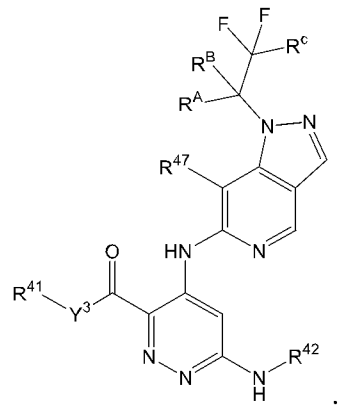
R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

30. The compound of claim 29, wherein Y^1 is CH and Y^2 is CH, having the structure:



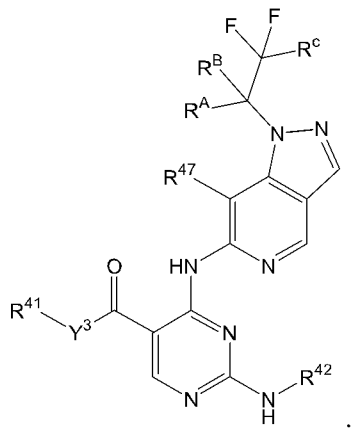
(III^a)

31. The compound of claim 29, wherein Y^1 is CH and Y^2 is N, having the structure:



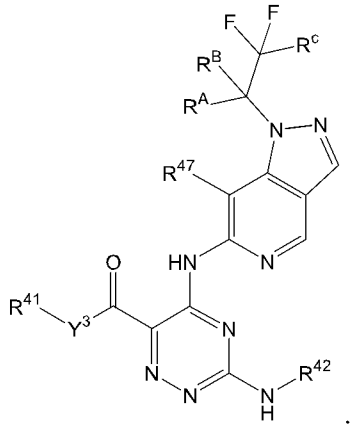
(III^b)

32. The compound of claim 29, wherein Y^1 is N and Y^2 is CH, having the structure:



(III^c)

33. The compound of claim 29, wherein Y^1 is N and Y^2 is N, having the structure:



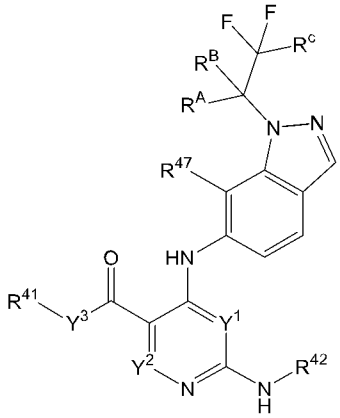
(III[d])

34. The compound of any one of claims 29-33, wherein R^A is H and R^B is H.

35. The compound of any one of claims 29-33, wherein one of R^A and R^B is not H.

36. The compound of any one of claims 29-35, wherein R^C is not CH_3.

37. A compound having the structural formula (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

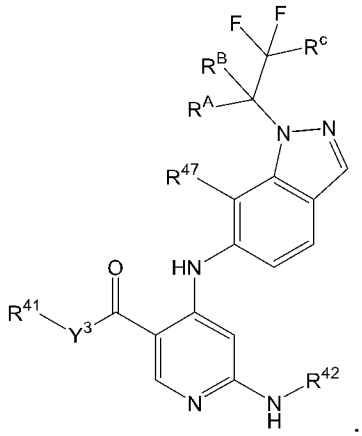
R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo.

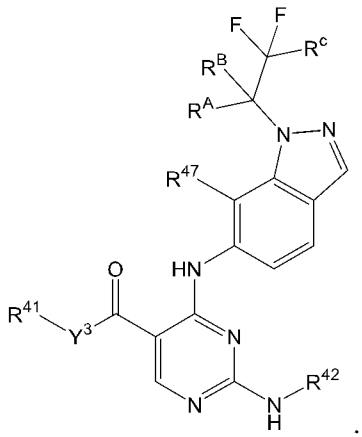
38. The compound of claim 37, wherein Y^1 is CH and Y^2 is CH, having the structure:



.

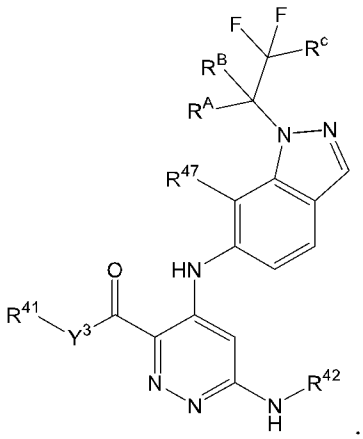
(IV[a])

39. The compound of claim 37, wherein Y^1 is N and Y^2 is CH, having the structure:



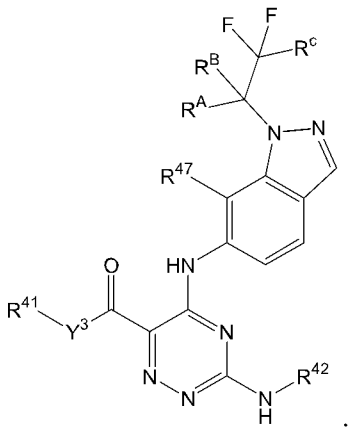
(IV[b])

40. The compound of claim 37, wherein Y^1 is CH and Y^2 is N, having the structure:



(IV[c])

41. The compound of claim 37, wherein Y^1 is N and Y^2 is N, having the structure:



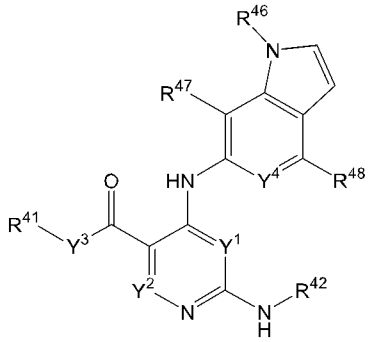
(IV^d)

42. The compound of any one of claims 37-41, wherein R^A is H and R^B is H.

43. The compound of any one of claims 37-41, wherein R^C is CH_3.

44. The compound of any one of claims 37-41, wherein R^C is not CH_3.

45. A compound having the structural formula (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

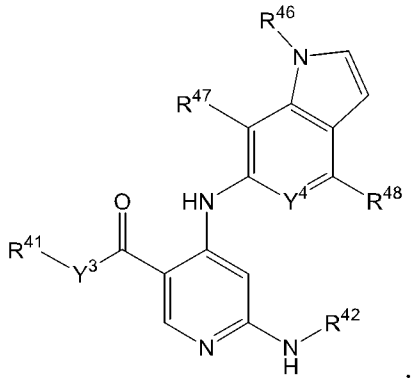
R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

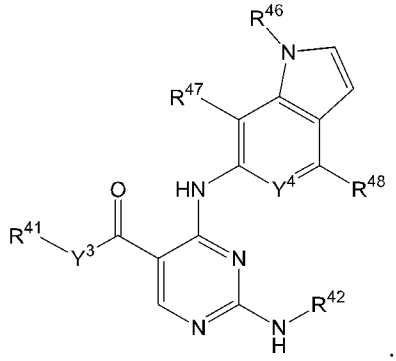
R^{48} is H, halo or a C_1-C_3 alkyl.

46. The compound of claim 45, wherein Y^1 is CH and Y^2 is CH, having the structure:



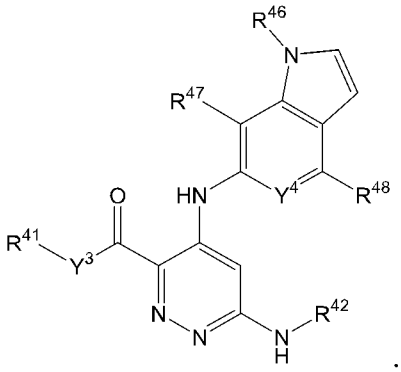
(V^a)

47. The compound of claim 45, wherein Y^1 is N and Y^2 is CH, having the structure:



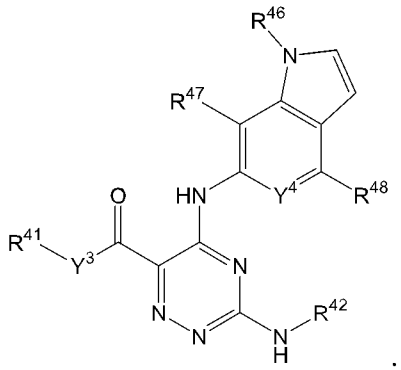
(V^b)

48. The compound of claim 45, wherein Y^1 is CH and Y^2 is N, having the structure:



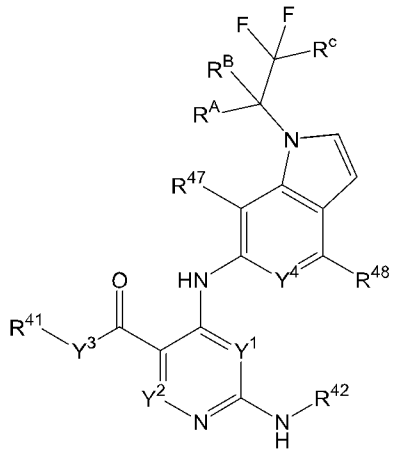
(V^c)

49. The compound of claim 45, wherein Y^1 is N and Y^2 is N, having the structure:



(V^d)

50. The compound of claim 45, having the structure:



(V^e)

wherein

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

51. The compound of any one of claims 45-50, wherein Y^4 is CH.
52. The compound of any one of claims 45-50, wherein Y^4 is N.
53. The compound of any one of claims 45-52, wherein R^{48} is H.
54. The compound of any one of claims 45-52, wherein R^{48} is halo.
55. The compound of any one of claims 1-54, wherein R^{47} is C_1-C_3 alkoxy.
56. The compound of any one of claims 1-54, wherein R^{47} is OCH_3.
57. The compound of any one of claims 1-54, wherein R^{47} is OCD_3.
58. The compound of any one of claims 1-57, wherein Y^3 is NR.
59. The compound of claim 58, wherein Y^3 is NH.
60. The compound of any one of claims 1-57, wherein Y^3 is O.
61. The compound of any one of claims 1-57, wherein Y^3 is O-NH.
62. The compound of any one of claims 1-61, wherein R^{41} is CH_3.
63. The compound of any one of claims 1-61, wherein R^{41} is CD_3.
64. The compound of any one of claims 1-63, wherein R^{42} is $R^{42'}$.
65. The compound of any one of claims 1-63, wherein R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is selected from C_1-C_6 alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{42c}.
66. The compound of claim 65, wherein R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is cyclopropyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.
67. The compound of claim 65, wherein R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is bis-spiro-cyclopropyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.
68. The compound of claim 65, wherein R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is cyclobutyl, optionally substituted with one or more of F, Cl, CH_3, CF_3 and CN.
69. The compound of claim 65, wherein R^{42} is $(C=O)R^{42b}$, wherein R^{42b} is C_1-C_6 alkyl, optionally substituted with one or more of F, Cl, CH_3, CF_3, CN, NRR' and OR.
70. The compound of any one of claims 1-63, wherein R^{42} is $(C=O)NHR^{42b}$, wherein R^{42b} is selected from C_1-C_6 alkyl, cyclopropyl or cyclobutyl, substituted with 0-2 R^{42c}.
71. The compound of any one of claims 1-63, wherein R^{42} is pyridinyl substituted with 0-2 R^{42c}.

72. The compound of any one of claims 1-63, wherein R^{42} is phenyl substituted with 0-2 R^{42c}.

73. The compound of any one of claims 1-63, wherein R^{42} is pyrazolyl substituted with 0-2 R^{42c}.

74. The compound of any one of claims 1-63, wherein R^{42} is pyrimidyl substituted with 0-2 R^{42c}.

75. The compound of any one of claims 71-74, wherein R^{42c} is CH_3 or CD_3.

76. The compound of any one of claims 71-74, wherein R^{42c} is F.

77. A compound selected from **Table 1A** or a pharmaceutically acceptable form or an isotope derivative thereof.

78. A compound selected from **Table 1B** or a pharmaceutically acceptable form or an isotope derivative thereof.

79. A pharmaceutical composition comprising a compound according to any of claims 1-78, 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.

80. The pharmaceutical composition of claim 79, being suitable for oral administration.

81. The pharmaceutical composition of claim 79 or 80, being suitable for topical administration.

82. The pharmaceutical composition of any one of claims 79-81, being suitable for GI-restricted administration.

83. The pharmaceutical composition of any one of claims 79-81, being useful to treat or reduce one or more of inflammatory diseases, immune-mediated diseases and cancers, or a related disease or disorder.

84. The pharmaceutical composition of claim 83, wherein the disease or disorder is an inflammatory disease.

85. The pharmaceutical composition of claim 84, wherein the disease or disorder is an immune-mediated disease.

86. The pharmaceutical composition of claim 84, wherein the disease or disorder is cancer.

87. The pharmaceutical composition of claim 86, 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.

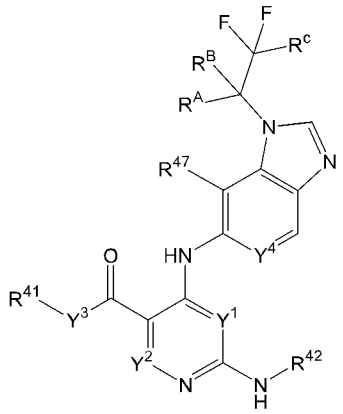
88. A unit dosage form comprising a pharmaceutical composition according to any of claims 79-87.

89. The unit dosage form of claim 88, being a tablet.

90. The unit dosage form of claim 88, being a capsule.

91. The unit dosage form of claim 88, being a topical formulation.

92. 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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a};

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

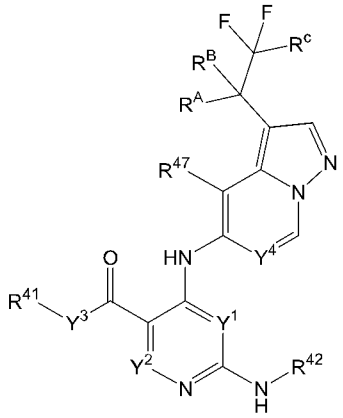
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

93. 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 (II):



(II)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

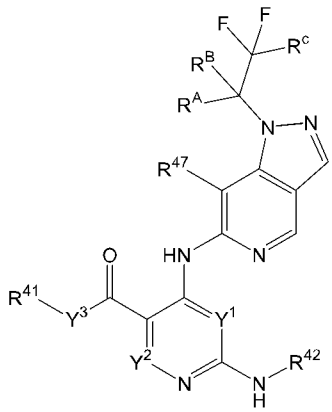
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

94. 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 (III):



(III)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not CH_3 or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

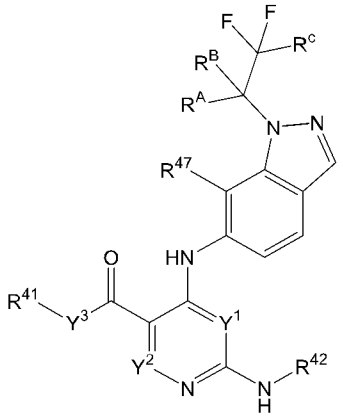
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

95. 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 (IV):



(IV)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a}; or

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R^A and R^B is independently selected from H, D, halo, OR, and C_{1-3} alkyl, provided that when both R^A and R^B is H, R^C is not H or F;

R^C is H, D, F, Cl, OR, C_{1-5} alkyl, C_{3-5} cycloalkyl or heterocyclic group, substituted with 0-2 R^{42a}.

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

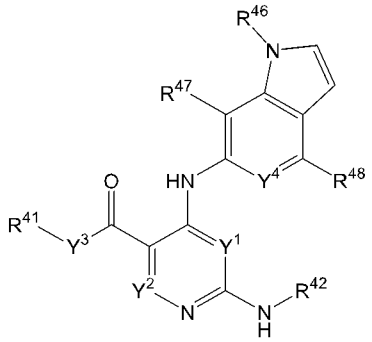
R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c}; and

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a}; and

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo,

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.

96. 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 (V):



(V)

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;

Y^4 is CH or N;

R^{41} is a H, F, C_1-C_3 alkyl and CD_3, provided that R^{41} is not F when Y^3 is NR, O or O-NH;

R^{42} is

$R^{42'}$, wherein $R^{42'}$ is a C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocycloalkyl, each substituted with 0-2 of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic, aryl and heteroaryl;

an aryl or heteroaryl group, each substituted with 0-2 R^{42a};

$(C=O)R^{42b}$; or

$(C=O)NHR^{42b}$;

each of R and R' is independently H or a C_1-C_6 alkyl, C_1-C_6 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;

R^{42a} at each occurrence is independently D, halo, OH, OR, CH_3, CF_3, CH_2CF_3, CN, C(O)NR, NRR', $(CH_2)_nNRR'$ or a 4- to 6-membered heterocycle having 1-4 heteroatoms selected from N, O and S;

R^{42b} is a C_{1-6} alkyl or C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-2 R^{42c};

R^{42c} at each occurrence is independently halo, CN, OR, NRR', OCF_3, CF_3, C_{1-6} alkyl substituted with 0-3 R^{42a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{42a}, C^{2-6} alkynyl substituted with 0-3 R^{42a};

R^{46} is H, CD_3, a C_1-C_6 alkyl or C_3-C_6 cycloalkyl, with 0-4 of halogen, CN and OR;

R^{47} is a C_{1-3} alkoxy group optionally substituted with 1-3 D or halo; and

R^{48} is H, halo or a C_1-C_3 alkyl,

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.

97. The method of any one of claims 92-96, wherein the disease or disorder is an inflammatory disease.

98. The method of any one of claims 92-96, wherein the disease or disorder is an immune-mediated disease.

99. The method of any one of claims 92-96, wherein the disease or disorder is cancer.

100. The method of any one of claims 92-99, 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.

101. The method of any of claims 92-100, wherein administration is via oral administration.
102. The method of any of claims 92-100, wherein administration is via topical administration.
103. The method of any of claims 92-100, wherein administration is via GI-restricted administration.
104. Use of a compound of any of claims 1-78, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.
105. The use of claim 104, wherein the disease or disorder is one or more of inflammatory diseases, immune-mediated diseases and cancer.
106. The use of claim 105, wherein the disease or disorder is an inflammatory disease.
107. The use of claim 105, wherein the disease or disorder is an immune-mediated disease.
108. The use of claim 105, wherein the disease or disorder is cancer.
109. The use of any one of claims 104-108, wherein the medicament is for oral administration.
110. The use of any one of claims 104-108, wherein the medicament is for topical administration.
111. The use of any one of claims 104-108, wherein the medicament is for GI restriction administration.
112. A method for preparing a compound of any one of claims 1-78.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/099407

A. CLASSIFICATION OF SUBJECT MATTER

C07D401/14(2006.01)i; C07D401/12(2006.01)i; C07D471/04(2006.01)i; A61K31/53(2006.01)i; A61P35/00(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:C07D, A61K, A61P

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,ENTXTC,WPABS,WPABSC,STN(REGISTRY,CAPLUS,MARPAT):LYNK,Li Xiaodong,SU Lin, benzimidazol, triazin+, amino, pyrazolo, pyrimidin,TYK,structural formulas (I)-(V)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2023109954 A1 (LYNK PHARMACEUTICALS CO., LTD.) 22 June 2023 (2023-06-22) claims 128-186,208,234-241, the description examples 131,266,276	1-111
X	CN 115466257 A (AIKENUO BIOMEDICAL (HONGKONG) CO., LTD.) 13 December 2022 (2022-12-13) claims 1,2,5-12, the description examples A2,A7,A9	1-111
A	CN 111484480 A (SHANGHAI HANSOH BIOMEDICAL CO., LTD. et al.) 04 August 2020 (2020-08-04) claims 1, 12,15-17	1-111
A	WO 2023278483 A1 (LOMOND THERAPEUTICS, INC.) 05 January 2023 (2023-01-05) claim 1	1-111
A	WO 2013117649 A1 (GALAPAGOS NV) 15 August 2013 (2013-08-15) claims 1, 21	1-111
A	WO 2013047813 A1 (TAIHO PHARMACEUTICAL CO., LTD.) 04 April 2013 (2013-04-04) claims 1-14	1-111

☑ 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	Date of mailing of the international search report
20 August 2024	**03 September 2024**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**HAN,WeiXiang** Telephone No. **(+86) 010-53962671**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013192049 A2 (PORTOLA PHARMACEUTICALS, INC.) 27 December 2013 (2013-12-27) claims 1-51	1-111
A	WO 2014081718 A1 (GENENTECH, INC.) 30 May 2014 (2014-05-30) claims 1-25	1-111

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/099407

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.: **92-103**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 92-103 relates to a method for treatment of human body by therapy as defined in PCT Rule 39.1(iv). This search report has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the corresponding diseases.

2. ☑ Claims Nos.: **112**
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 112 relates to a method for preparing a compound of any one of claims 1-78 without any technical features of preparation. Thus, no meaningful international search according to claim 112 can be carried out.

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/CN2024/099407

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2023109954 A1	22 June 2023	TW 202339749 A	16 October 2023
		US 2024124448 A1	18 April 2024
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CN 115466257 A	13 December 2022	None	
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		EP 3181564 A1	21 June 2017
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		KR 20150087850 A	30 July 2015