JAK inhibitors. *Enhanced Efficacy*: By concentrating the therapeutic effect within the gut, gastrointestinal restricted or enriched JAK inhibitors may provide enhanced efficacy in controlling inflammation and promoting mucosal healing in patients with IBD and Crohn's disease. *Reduced Systemic Side Effects*: The localized action of these inhibitors may lead to a reduced incidence of systemic adverse effects such as infections or hematologic abnormalities, which are associated with systemic JAK inhibitors. *Potential for Lower Doses*: Targeting JAK inhibition to the gastrointestinal tract may allow for lower doses of medication to achieve therapeutic effects, further reducing the risk of systemic side effects. *Combination Therapy*: Gastrointestinal restricted or enriched JAK inhibitors can be used alone or in combination with other therapies for IBD management, offering flexibility in treatment approaches while potentially minimizing systemic exposure to medications.

[010] Solubility is a critical factor in the development of small molecule drugs as it directly impacts their bioavailability, efficacy, and ultimately, their clinical success. Poor solubility can lead to insufficient drug absorption, erratic pharmacokinetics, and reduced therapeutic effectiveness. Consequently, enhancing solubility is a primary focus in drug development to ensure adequate drug delivery and optimal therapeutic outcomes. Several drug candidates have faced setbacks or failures in clinical development due to solubility issues. These cases underscore the importance of addressing solubility early in the drug development process to mitigate risks and optimize the clinical potential of small molecule therapeutics.

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

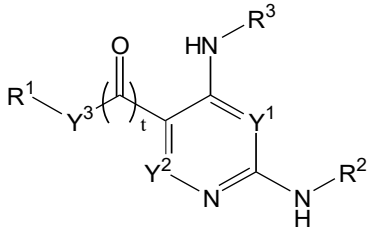
Summary

[012] The disclosure provides novel, selective and potent compounds that are orally and/or topically available and/or suitable for CNS penetrable, gastrointestinal (GI) tract restricted and/or topical administration. These therapeutic agents are safe and effective TYK2 inhibitors and may exhibit fewer and/or lesser side effects than currently available drugs. The disclosure also provides pharmaceutical compositions of these compounds and methods of their preparation and use.

[013] Disclosed herein are a series of novel TYK2 inhibitors that were specifically designed to fit in the profiles that are potentially suitable for (I) CNS penetrable or (II) oral administrations

or (III) GI and/or skin topical uses. For compounds designed for oral administration, they are potent for TYK2 with an array of selectivity against other JAK kinases and JAK1 JH2 domain with good overall drug profiles. For the compounds that are potentially suitable for GI restricted use, their properties such as Caco-2 data, solubility, PK *etc*. are suitable for limiting them to the intestinal action site. For the compounds that are potentially suitable for topical uses, they are designed to have good skin permeability and high retention amount in epidermis and dermis. The new class of inhibitors exhibits exceptional potency profiles with TYK2 IC50 values in the low picomolar or nanomolar range. These therapeutic agents are safe and effective TYK2 inhibitors and exhibit fewer and/or lesser side effects than currently available drugs. The disclosure also provides pharmaceutical compositions of these compounds and methods of their preparation and use.

[014] The disclosure 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, CD_2, CF_2 or O-NH;

t is 0 or 1;

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

R^2 is

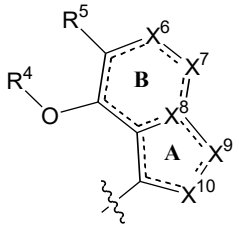
$R^{2'}$, wherein $R^{2'}$ is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_5-C_7 spirocycloalkyl, or C_3-C_6 heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl, heterocyclic;

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

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

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

R^3 is



(**II**)

wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

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

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

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

R^{2b} is a C$_{1-6}$ alkyl or C$_{3-6}$ cycloalkyl, C$_{5-7}$ spirocycloalkyl, aryl or heteroaryl, each substituted with 0-4 R^{2c};

R^{2c} at each occurrence is independently halo, CN, OR, NRR', OCF$_3$, CF$_3$, C$_{1-6}$ alkyl, C$_{1-6}$ haloalkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, wherein said alkyl, haloalkyl, alkenyl, alkynyl, R and R' are substituted with 0-3 R^{2a}; and

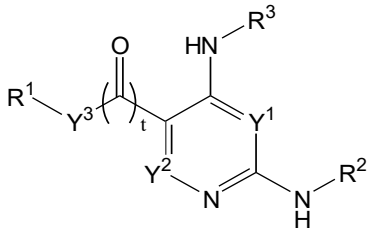
R^4 is a C$_{1-3}$ alkyl, substituted with 0-5 R^{4a}, wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH$_3$, C(=O)OR, NHC(=O)R, NRR', NO$_2$, C$_{1-6}$ alkyl, C$_3$-C$_6$ cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a}, wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, CH$_2$F, CHF$_2$, CF$_3$, OCH$_3$, OCD$_3$, OCF$_3$ and OC(=O)CH$_3$;

each of R^6, R^7, R^9 and R^{10} is independently selected from H, F, Cl, CN, CD$_3$, CH$_2$CF$_3$, CF$_3$, OR, NRR', C$_1$-C$_3$ alkyl and C$_3$-C$_5$ cycloalkyl, wherein said alkyl, cycloalkyl, R and R' are substituted with 0-2 R^{2a}; and

each of R and R' is independently H or a C$_1$-C$_6$ alkyl or acyl, or R and R', together with the nitrogen atom to which they are bonded, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO$_2$.

[014] In an aspect, the disclosure provides a compound having the structural formula (I):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2, CD_2, CF_2 or O-NH;

t is 0 or 1;

R^1 is H, F, CD_3, or $C_{1\text{-}3}$ alkyl, provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

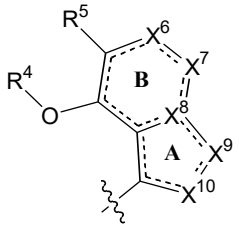
$R^{2'}$, wherein $R^{2'}$ is C_1-C_6 alkyl, $C_{3\text{-}6}$ cycloalkyl, $C_{5\text{-}7}$ spirocycloalkyl, or $C_{3\text{-}6}$ heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl and heterocycle;

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

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

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

R^3 is



(**II**)

wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

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

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

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

R^{2b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-4 R^{2c};

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

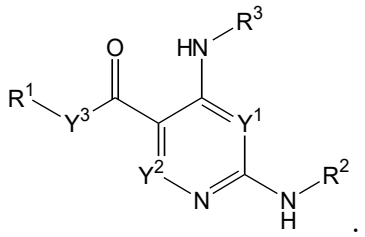
R^4 is C_{1-3} alkyl, substituted with 0-5 R^{4a}, wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3, C(=O)OR, NHC(=O)R, NRR', NO_2, C_{1-6} alkyl, C_{3-6} cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a}, wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, CH_2F, CHF_2, CF_3, OCH_3, OCD_3, OCF_3 and $OC(=O)CH_3$;

each of R^6, R^7, R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3, CH_2CF_3, CF_3, OR, NRR', C_{1-3} alkyl and C_{3-5} cycloalkyl, wherein said alkyl, cycloalkyl, R and R' are substituted with 0-2 R^{2a}; and

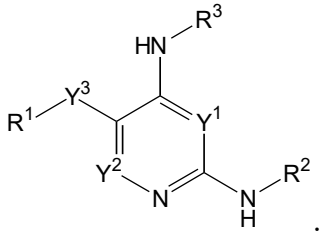
each of R and R' is independently H or a C_1-C_6 alkyl or acyl, or R and R', together with the nitrogen atom to which they are bonded, form a 4- to 7-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2.

[015] In certain examples of (**I**), *t* is 1, and the compound has the structural formula:



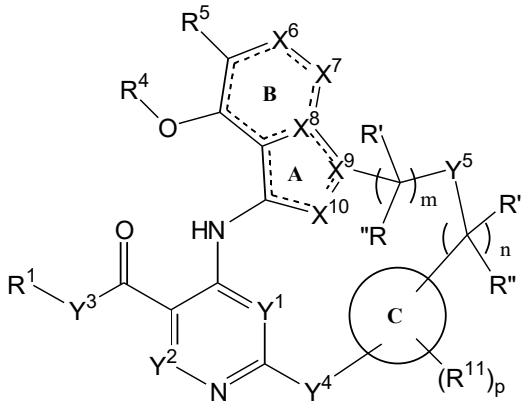
(**III**^{a})

[016] In certain examples of (**I**), *t* is 0, and the compound has the structural formula:



(**III**^{b})

[017] In another example, the disclosure generally relates to a compound having the structural formula (**VIII**):



(**VIII**)

or a pharmaceutically acceptable form or an isotope derivative thereof,

wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

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

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

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2, CD_2, CF_2 or O-NH;

Y^4 is NR, CH_2 or CF_2;

Y^5 is NR, CH_2, O, S, SO or SO_2;

m is 0, 1, 2 and 3;

n is 0, 1, 2 and 3;

p is 0, 1, 2 and 3;

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

Ring C is a 5- or 6-membered aryl or heteroaryl group;

R^1 is H, F, CD_3, or C_{1-3} alkyl, provided that R^1 is not F when Y^3 is N, O or O-NH;

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

R^5 is H, CN, halo, OCH_3, C(=O)OR, NHC(=O)R, NRR', NO_2, C_{1-6} alkyl, C_{3-6} cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a}, wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, CH_2F, CHF_2, CF_3, OCH_3, OCD_3, OCF_3 and $OC(=O)CH_3$;

each of R^6, R^7, R^9, R^{10} and R^{11} is independently selected from H, F, Cl, CN, CD_3, CH_2CF_3, CF_3, OR, NRR', C_{1-3} alkyl and C_{3-5} cycloalkyl, wherein said alkyl, cycloalkyl, R and R' are substituted with 0-2 R^{2a};

R^{2a} is selected from F, OCF_3, CF_3, CN, NO_2, OR, NRR' and C_{1-6} alkyl; and

each of R and R' independently H, C_1-C_6 alkyl or acyl, or R and R' together with the nitrogen or carbon atom to which they are bonded, form a 3- to 6-membered ring comprising 0-2 heteroatoms selected from O, NR, S and SO_2.

[017a] In another aspect, the disclosure provides a compound selected from Table 1 or a pharmaceutically acceptable salt thereof.

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

[019] In yet another example, the disclosure 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.

[019a] In another aspect, the disclosure provides a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, or diluent.

[020] In yet another example, the disclosure generally relates to a unit dosage form comprising a pharmaceutical composition disclosed herein.

[021] In yet another example, the disclosure 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 disclosed herein, 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.

[021a] In another aspect, the disclosure provides a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in therapy.

[022] In yet another example, the disclosure 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.

[022a] In another aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating or reducing one or more diseases or disorders in a mammal.

Brief Description of the Drawings

[023] **FIG. 1** shows certain exemplary data on changes in mouse weight (A) and DAI score (B). n = 10 mice per group, data are shown as mean values ± SEM are presented, * $p<0.05$, ** $p<0.01$, *** $p<0.005$, **** $p<0.0001$, versus Vehicle, two way-ANOVA, Dunnet's test for multiple comparisons.

[024] **FIG. 2** shows certain exemplary data on changes in mouse weight (A) and DAI score (B). n = 8 mice per group, data are shown as mean values ± SEM are presented, * $p<0.05$, ** $p<0.01$, *** $p<0.005$, **** $p<0.0001$, versus Vehicle, two way-ANOVA, Dunnet's test for multiple comparisons.

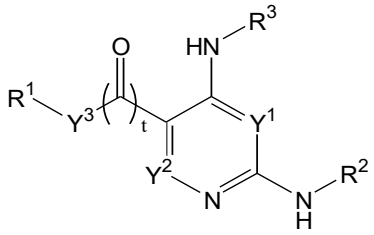
[025] **FIG. 3** shows certain exemplary data on immune cells in whole blood. n = 5 mice per group, data are shown as mean values ± SEM are presented, * $p<0.05$, ** $p<0.01$, *** $p<0.005$, **** $p<0.0001$, versus Vehicle, two way-ANOVA, Dunnet's test for multiple comparisons.

[026] **FIG. 4** shows certain exemplary data on $CD4^+$T cell count (A) and histology score in colon (B). n = 8 mice per group, data are shown as mean values ± SEM are presented, * $p<0.05$, ** $p<0.01$, *** $p<0.005$, **** $p<0.0001$, versus Vehicle, two way-ANOVA, Dunnet's test for multiple comparisons.

What is claimed is:

CLAIMS

1. A compound having the structural formula (I):



(**I**)

or a pharmaceutically acceptable salt thereof,

wherein

Y^1 is CH, CF or N;

Y^2 is CH or N;

Y^3 is NR, O, CH_2, CD_2, CF_2 or O-NH;

t is 0 or 1;

R^1 is H, F, CD_3, or $C_{1\text{-}3}$ alkyl, provided that R^1 is not F when Y^3 is N, O or O-NH;

R^2 is

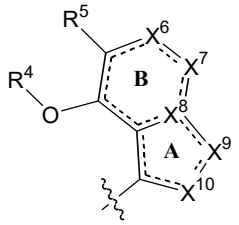
$R^{2'}$, wherein $R^{2'}$ is C_1-C_6 alkyl, $C_{3\text{-}6}$ cycloalkyl, $C_{5\text{-}7}$ spirocycloalkyl, or $C_{3\text{-}6}$ heterocycloalkyl, each substituted with 0-2 R^{2a}, wherein R^{2a} is selected from the group consisting of halogen, CN, OR, NRR', alkyl, cycloalkyl and heterocycle;

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

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

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

R^3 is



(**II**)

wherein

X^6 is CR^6 or N;

X^7 is CR^7 or N;

X^8 is C or N;

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

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

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

R^{2b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{5-7} spirocycloalkyl, aryl or heteroaryl, each substituted with 0-4 R^{2c};

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

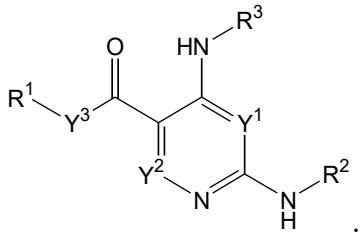
R^4 is C_{1-3} alkyl, substituted with 0-5 R^{4a}, wherein R^{4a} is selected from D, F and Cl;

R^5 is H, CN, halo, OCH_3, C(=O)OR, NHC(=O)R, NRR', NO_2, C_{1-6} alkyl, C_{3-6} cycloalkyl or heterocyclic, wherein said alkyl, cycloalkyl or heterocyclic is substituted with 0-3 R^{5a}, wherein each R^{5a} is independently selected from OH, D, F, Cl, CN, CH_2F, CHF_2, CF_3, OCH_3, OCD_3, OCF_3 and $OC(=O)CH_3$;

each of R^6, R^7, R^9 and R^{10} is independently selected from H, F, Cl, CN, CD_3, CH_2CF_3, CF_3, OR, NRR', C_{1-3} alkyl and C_{3-5} cycloalkyl, wherein said alkyl, cycloalkyl, R and R' are substituted with 0-2 R^{2a}; and

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

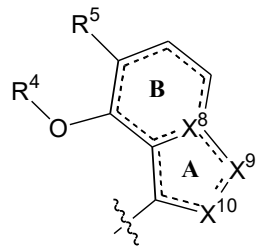
2. The compound of claim 1, having the following structural formula, or a pharmaceutically acceptable salt thereof:



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(**III^a**)

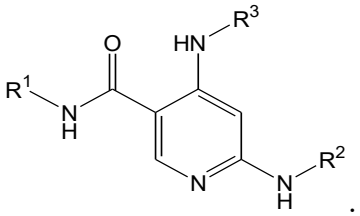
3. The compound of claim 1, wherein R^3 has the following structural formula:



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(**II^a**)

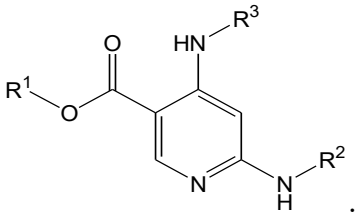
4. The compound of claim 1, having the following structural formula, or a pharmaceutically acceptable salt thereof:



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(**IV^a**)

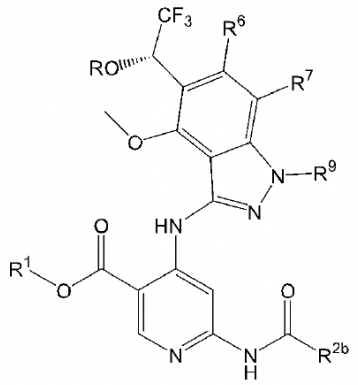
5. The compound of claim 1, having the following structural formula, or a pharmaceutically acceptable salt thereof:

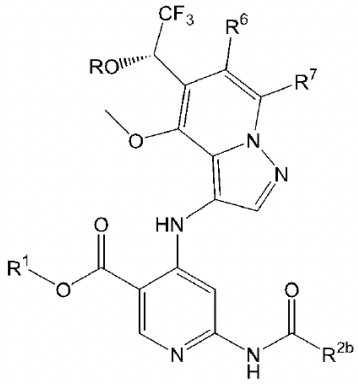


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(**V^a**)

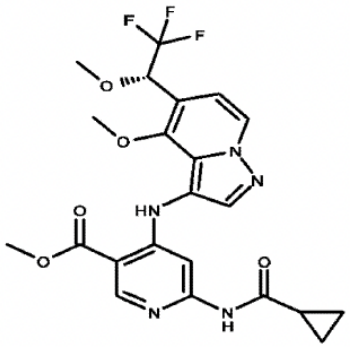
6. The compound of claim 1, having one of the following structural formulas, or a pharmaceutically acceptable salt thereof:

V^{20} , and

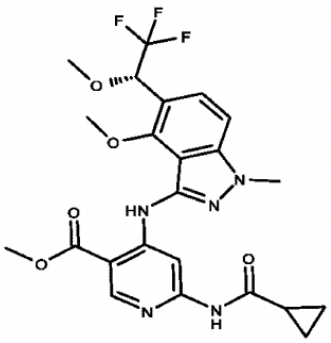
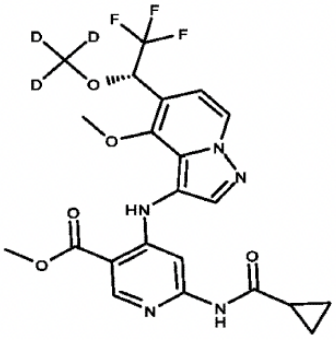
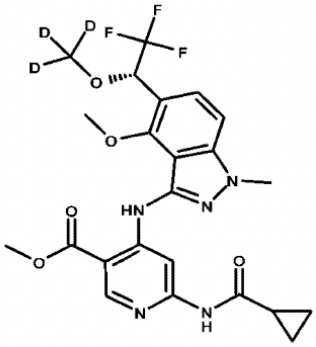
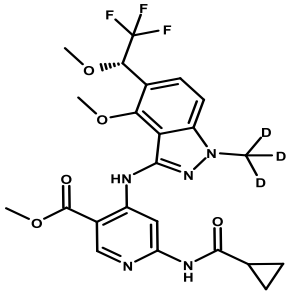
V^{22} .

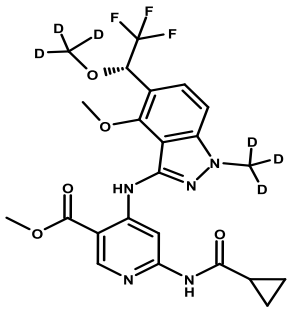
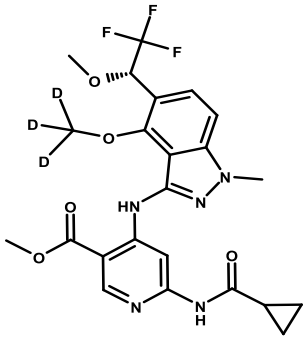
7. A compound selected from **Table 1** or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is selected from one of the following compounds, or a pharmaceutically acceptable salt thereof:

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

45B		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-1-methyl-5-(2,2,2-trifluoro-l-methoxyethyl)-lH-indazol-3-yl)amino)nicotinate,
47		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-5-(2,2,2-trifluoro-l-(methoxy-d3)ethyl)pyrazolo[1,5-a]pyridin-3-yl)amino)nicotinate, and
50B		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-l-methyl-5-(2,2,2-trifluoro-1-(methoxy-d3)ethyl)-lH-indazol-3-yl)amino)nicotinate.
52A		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-1-(methyl-d3)-5-(2,2,2-trifluoro-1-methoxyethyl)-1H-indazol-3-yl)amino)nicotinate

53B		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-methoxy-1-(methyl-d3)-5-(2,2,2-trifluoro-1-(methoxy-d3)ethyl)-1H-indazol-3-yl)amino)nicotinate
120A		Methyl (S)-6-(cyclopropanecarboxamido)-4-((4-(methoxy-d3)-1-methyl-5-(2,2,2-trifluoro-1-methoxyethyl)-1H-indazol-3-yl)amino)nicotinate

9. A pharmaceutical composition comprising a compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, or diluent.
10. A compound according to any one of claims 1-8, or a pharmaceutical composition according to claim 9, for use in therapy.
11. Use of a compound of any one of claims 1-8, or a pharmaceutical composition of claim 9, in the preparation of a medicament for treating or reducing one or more diseases or disorders in a mammal.