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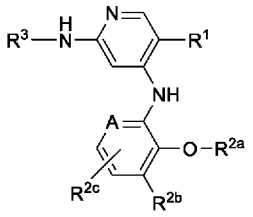

(I)

(57) Abstract: Compounds having the structure of Formula (I) or pharmaceutically acceptable isomers, racemates, hydrates, solvates or salts thereof, where A, R^1, R^{2a}, R^{2b}, R^{2c} and R^3 are as defined herein, are useful in the modulation of IL-12, IL-23 and/or IFNα by acting on TYK2 to cause signal transduction inhibition, as well as to pharmaceutical compositions containing the same and to methods of their use and preparation.

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SUBSTITUTED PYRIDINES

BACKGROUND OF THE DISCLOSURE

[0001] The present invention generally relates to compounds useful in the modulation of IL-12, IL-23 and/or IFNα by acting on TYK2 to cause signal transduction inhibition, as well as to pharmaceutical compositions containing the same and to methods of their use and preparation.

BACKGROUND

[0002] Janus kinases (or JAK's) are an intracellular, non-receptor tyrosine kinase family consisting of four different subtypes, namely JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAK1, JAK2, and TYK2 are ubiquitously expressed, while JAK3 expression is limited to leukocytes. Cytokines mediate a broad range of biological functions and play pivotal roles in immunity and inflammation by regulating the survival, proliferation, differentiation and function of immune cells, as well as cells from other organ systems. JAKs bind to various cytokine receptors (interleukins, interferons and hemoproteins), leading to tyrosine phosphorylation and thereby activation of STAT (signal transducers and activators of transcription) proteins and ultimately transcriptional activation of specific genes. Thus, JAKs play a key role in modulating immune and inflammatory responses to a variety of cytokines.

[0003] The JAK proteins are relatively large (120-140kDa), with defined structures featuring seven distinct regions named Janus Homology domains 1-7 (JH1-7). Cytokine receptors typically functional as heterodimers, and as a result, more than one type of JAK kinase is often associated with cytokine receptor complexes.

[0004] **JAK1** associates with the type I interferon (e.g., IFNα), type II interferon (e.g., IFNγ), IL-2 and IL-6 cytokine receptor complexes. JAK1 knockout mice die perinatally from defects in LIP receptor signaling.

[0005] **JAK2** associates with single-chain (e.g., EPO), IL-3 and interferon gamma cytokine receptor families. JAK2 knockout mice die of anemia and kinase activating

mutations in JAK2 (e.g., JAK2 V617F) are associated with myeloproliferative disorders (MPDs). Complete JAK2 inhibition leads to thrombocytopenia.

[0006] **JAK3** associates exclusively with the gamma common cytokine receptor chain, present in the IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 cytokine receptor complexes. JAK3 is critical for lymphoid cell development and proliferation. Mutations in JAK3 result in severe combined immunodeficiency (SCID). JAK3 and JAK3-mediated pathways have been targeted for immunosuppressive indications (e.g., transplantation rejection and rheumatoid arthritis).

[0007] **TYK2** associates with the type I interferon (e.g., IFNα), IL-6, IL-10, IL-12 and IL-23 cytokine receptor complexes, particularly IL12, IL23 and IFNα. Primary cells derived from a TYK2 deficient human are defective in type I interferon, IL-6, IL-10, IL-12 and IL-23 signaling. TYK2 −/− mice are resistant to experimental arthritis, non-responsive to small amounts of IFN-α, and exhibit abnormal responses to inflammatory challenges. TYK2 plays an important role in immunity to infection, and autoimmune and inflammatory diseases. Further, TYK2 activating mutants and fusion proteins have been detected in patients with leukemic diseases suggesting TYK2 is a potent oncogene. Tumor immune surveillance is the immune system's ability to identify and subsequently eliminate cancerous self, thus counteracting spontaneous cellular mutations that otherwise would have targeted proto-oncogenes or tumor suppressor genes. TYK2 is associated with tumor surveillance and carcinogenesis. (see Leitner *et al*, "Tyrosine kinase 2- surveillant of tumors and bona fide oncogene", Cytokine **2017**, *89*, 209−218).

[0008] JAK's as therapeutic targets have been explored and validated. Approved JAK inhibitor drugs include:

- Ruxolitinib (Jakafi®) is a JAK1/2 dual inhibitor indicated for the treatment of polycythemia vera (PV), intermediate or high-risk myelofibrosis (MF), and steroid-refractory acute graft-versus-host disease (GVHD).
- Baricitinib (Olumiant®) is a JAK1/2 dual inhibitor for the treatment of rheumatoid arthritis (RA), atopic dermatitis and systemic lupus erythematosus.

Tofacitinib (Xeljanz®) is a pan-JAK inhibitor for the treatment of moderate to severe rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis.

Ustekinumab (Stelara®) is a human IgG1κ monoclonal antibody targeting the p40 subunit of the IL-12 and IL-23 cytokines for treatment of moderate to severe active Crohn's disease, moderate to severe active ulcerative colitis, moderate or severe psoriasis and active psoriatic arthritis.

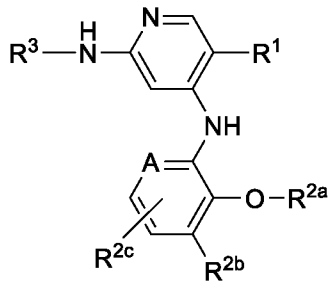
[0009] Side effects of these drugs can be very serious and include infections (pneumonia, herpes zoster, UTI, tuberculosis, candidiasis, pneumocystosis, bacterial, viral and other infections), malignancy (lymphoma) and thrombosis (deep venous thrombosis (DVT) pulmonary embolism (PE), arterial thrombosis).

[0010] Studies have shown that inhibition of TYK2 can regulate interleukin-12 (IL12), interleukin-23 (IL23) and type I interferon (IFNα), while leaving other cytokines unaffected would minimize side effects. As such, *selective* inhibition of TYK2 is a potential therapeutic strategy for treatment of diseases related to regulation of IFNα, IL12, and IL23, while minimizing the side effects of other JAK family subtypes. Notably, no small molecule TYK2 inhibitor has been approved for therapeutic use. There is, therefore, a need for *selective* inhibitors of TYK2.

[0011] Described herein are compounds that modulate IL-12, IL-23 and/or IFNα by acting on TYK2, and methods for using them to treat diseases, conditions, syndromes, and the like, that are affected by 12, IL-23 and/or IFNα levels. Regulation of these factors may provide methods for re-balancing or regulating one or more biological pathways associated with abnormal conditions, particularly autoimmune disorders, such as but not limited to Psoriasis, Psoriatic Arthritis, Atopic Dermatitis, Crohn's Disease, Ulcerative Colitis, Lupus Nephritis, Systemic lupus erythematosus (SLE), Alopecia Areata, Vitiligo and Hidradenitis Suppurativa. Also described herein are pharmaceutical compositions containing at least one compound according to the invention that are useful for the treatment of conditions related to the modulation of IL-12, IL-23 and/or IFNα. Also described are methods for the preparation of the compounds of Formula (I).

BRIEF SUMMARY

[0012] In one embodiment, compounds are provided having the structure of Formula (I):

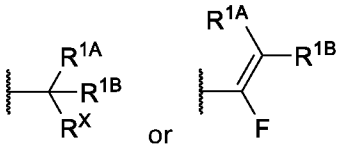


(I)

or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, or salt thereof, wherein:

A is N or CR^{2c};

R^1 is



wherein

R^x is F, O-R^{1C} or N(R^{1C})R^{1D};

R^{1A} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1B} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1C} is H,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1D} is H,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$; or

R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3 to 6 membered ring, optionally containing an O, N or S atom;

and wherein R^1 comprises at least one Fluorine atom;

R^{2a} is H, C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^{2b} is H, −CN, −C(O)OH, −C(O)OC_{1-4}alkyl, −C(O)NR^5R^6, or 5- or 6-membered heteroaryl, wherein R^{2b} is substituted with 0-2 R';

R^{2c} is H, halo, −CN, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4}haloalkyl;

R^3 is H, C_{2-4} alkoxy, −C(O)R^7, carbocycle, heterocycle, aryl or heteroaryl, wherein R^3 is substituted with 0-2 R';

R^5 is H or C_{1-4} alkyl;

R^6 is H, C_{1-4} alkyl, −$(CH_2)_m$−carbocycle, −$(CH_2)_m$−heterocycle, −$(CH_2)_m$−aryl or −$(CH_2)_m$−heteroaryl;

R^7 is C_{1-4} alkyl, −$(CH_2)_n$−OH, −$(CH_2)_n$−OC_{1-4}alkyl, −$(CH_2)_n$−NH_2, −$(CH_2)_n$−NHC_{1-4}alkyl, −$(CH_2)_n$−N(C_{1-4}alkyl)(C_{1-4}alkyl), −$(CH_2)_n$−carbocycle, −$(CH_2)_n$−heterocycle , −$(CH_2)_m$−aryl, −$(CH_2)_m$−heteroaryl or halocycloalkyl, wherein R^7 is substituted with 0-2 R';

R' is −CN, −NO_2, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, alkoxyalkyl, carbocycle, −$(CH_2)_q$−NRR, −$(CH_2)_q$−C(O)R, −$(CH_2)_q$−C(O)OR, −$(CH_2)_q$−C(O)NRR, −$(CH_2)_q$−NHC(O)R, −$(CH_2)_q$−S(O)$_2$R, -$(CH_2)_q$-carbocycle or -$(CH_2)_q$-heterocycle;

each R is, independently, H, C_{1-4} alkyl, haloalkyl, carbocycle or heterocycle;

m is 0-2;

n is 0-2; and

q is 0-4.

[0013] In another embodiment, compounds are provided having the structure listed in Table 1, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.

[0014] In another embodiment, a composition is provided, comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer,

racemate, hydrate, solvate, isotope, or salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0015] In another embodiment, a use is provided, for a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof in the manufacture of a medicament.

[0016] In another embodiment, a method for inhibiting tyrosine kinase 2 (TYK2) activity is provided, comprising contacting the TYK with an effective amount of a compound having the structure of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof

[0017] In another embodiment, a method for inhibiting tyrosine kinase 2 (TYK2) activity in a subject is provided, comprising administering to the subject an effective amount of a compound having the structure of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof.

[0018] In another embodiment, a method for modulating IL-12, IL-23 and/or IFNα is provided, comprising contacting the IL-12, IL-23 and/or IFNα with an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof.

[0019] In another embodiment, a method is provided for treating a subject with Psoriasis, Psoriatic Arthritis, Atopic Dermatitis, Crohn's Disease, Ulcerative Colitis, Lupus Nephritis, Systemic lupus erythematosus (SLE), Alopecia Areata, Vitiligo or Hidradenitis Suppurativa is provided, comprising administering to the subject an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof.

[0020] In another embodiment, a method is provided for treating Psoriasis, Psoriatic Arthritis, Atopic Dermatitis, Crohn's Disease, Ulcerative Colitis, Lupus Nephritis, Systemic lupus erythematosus (SLE), Alopecia Areata, Vitiligo or Hidradenitis Suppurativa, comprising administering to a subject an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, isomer, tautomer, racemate, or isotope thereof.

DETAILED DESCRIPTION

[0021] The present invention relates to pyridine compounds, pharmaceutical compositions containing them, methods of using them for the treatment of disease states, disorders and conditions related to the modulation of TYK2, IL-12, IL-23 and/or IFNα and methods for preparing them.

[0022] As used herein, "alkyl" means a straight chain or branched saturated hydrocarbon group. "Lower alkyl" means a straight chain or branched alkyl group having from 1 to 8 carbon atoms, in some embodiments from 1 to 6 carbon atoms, in some embodiments from 1 to 4 carbon atoms, and in some embodiments from 1 to 2 carbon atoms. Examples of straight chain lower alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched lower alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups.

[0023] "Alkenyl" groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to $-CH=CH2$, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, $-CH=CHCH_2CH_3$, $-CH=CH(CH_2)_2CH_3$, $-CH=CH(CH_2)_3CH_3$, $-CH=CH(CH_2)_4CH_3$, vinyl, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

[0024] "Alkynyl" groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to $-C\equiv CH$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-CH_2C\equiv CH$, $-CH_2C\equiv C(CH_3)$, and $-CH_2C\equiv C(CH_2CH_3)$, among others.

[0025] As used herein, "alkylene" means a divalent alkyl group. Examples of straight chain lower alkylene groups include, but are not limited to, methylene (i.e., $-CH_2-$),

ethylene (i.e., $-CH_2CH_2-$), propylene (i.e., $-CH_2CH_2CH_2-$), and butylene (i.e., $-CH_2CH_2CH_2CH_2-$). As used herein, "heteroalkylene" is an alkylene group of which one or more carbon atoms is replaced with a heteroatom such as, but not limited to, N, O, S, or P.

[0026] "Alkoxy" refers to an alkyl as defined above joined by way of an oxygen atom (i.e., −O−alkyl). Examples of lower alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, n-butoxy, isopropoxy, sec-butoxy, tert-butoxy, and the like.

[0027] The terms "carbocyclic" and "carbocycle" denote a ring structure wherein the atoms of the ring are carbon. Carbocycles may be monocyclic or polycyclic. Carbocycle encompasses both saturated and unsaturated rings. Carbocycle encompasses both cycloalkyl and aryl groups. In some embodiments, the carbocycle has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms is 4, 5, 6, or 7. Unless specifically indicated to the contrary, the carbocyclic ring can be substituted with as many as N substituents wherein N is the size of the carbocyclic ring with for example, alkyl, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

[0028] "Cycloalkyl" groups are alkyl groups forming a ring structure, which can be substituted or unsubstituted. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or

cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

[0029] "Aryl" groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Thus, aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons in the ring portions of the groups. The terms "aryl" and "aryl groups" include include fused rings wherein at least one ring, but not necessarily all rings, are aromatic, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like).

[0030] "Carbocyclealkyl" refers to an alkyl as defined above with one or more hydrogen atoms replaced with carbocycle. Examples of carbocyclealkyl groups include but are not limited to benzyl and the like.

[0031] As used herein, "heterocycle" or "heterocyclyl" groups include aromatic and non-aromatic ring compounds (heterocyclic rings) containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, S, or P. A heterocycle group as defined herein can be a heteroaryl group or a partially or completely saturated cyclic group including at least one ring heteroatom. In some embodiments, heterocycle groups include 3 to 20 ring members, whereas other such groups have 3 to 15 ring members. At least one ring contains a heteroatom, but every ring in a polycyclic system need not contain a heteroatom. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocycle groups within the meaning herein. A heterocycle group designated as a C2-heterocycle can be a 5-membered ring with two carbon atoms and three heteroatoms, a 6-membered ring with two carbon atoms and four heteroatoms and so forth. Likewise, a C4-heterocycle can be a 5-membered ring with one heteroatom, a 6-membered ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A saturated heterocyclic ring refers to a heterocyclic ring containing no unsaturated carbon atoms.

[0032] "Heteroaryl" groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. A heteroaryl group designated as a C_2-heteroaryl can be a 5-membered ring with two carbon atoms and three heteroatoms, a 6-membered ring with two carbon atoms and four heteroatoms and so forth. Likewise, a C_4-heteroaryl can be a 5-membered ring with one heteroatom, a 6-membered ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinoxalinyl, and quinazolinyl groups. The terms "heteroaryl" and "heteroaryl groups" include fused ring compounds such as wherein at least one ring, but not necessarily all rings, are aromatic, including tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl and 2,3-dihydro indolyl.

[0033] "Heterocyclealkyl" refers to an alkyl as defined above with one or more hydrogen atoms replaced with heterocycle. Examples of heterocyclealkyl groups include, but are not limited to, morpholinoethyl and the like.

[0034] "Halo" or "halogen" refers to fluorine, chlorine, bromine and iodine.

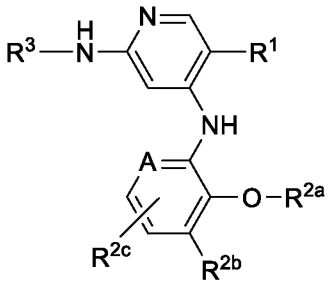
[0035] "Haloalkyl" refers to an alkyl as defined above with one or more hydrogen atoms replaced with halogen. Examples of lower haloalkyl groups include, but are not limited to, $-CF_3$, $-CH_2CF_3$, and the like.

[0036] "Haloalkoxy" refers to an alkoxy as defined above with one or more hydrogen atoms replaced with halogen. Examples of lower haloalkoxy groups include, but are not limited to $-OCF_3$, $-OCH_2CF_3$, and the like.

[0037] "Hydroxyalkyl" refers to an alkyl as defined above with one or more hydrogen atoms replaced with −OH. Examples of lower hydroxyalkyl groups include, but are not limited to $-CH_2OH$, $-CH_2CH_2OH$, and the like.

[0038] As used herein, the term "optionally substituted" refers to a group (e.g., an alkyl, carbocycle, or heterocycle) having 0, 1, or more substituents, such as 0-25, 0-20, 0-10 or 0-5 substituents. Substituents include, but are not limited to $-OR^x$, $-NR^xR^y$, $-S(O)_2R^x$ or $-S(O)_2OR^x$, halogen, cyano, alkyl, haloalkyl, alkoxy, carbocycle, heterocycle, carbocyclalkyl, or heterocyclealkyl, wherein each R^x and R^y is, independently, H, alkyl, haloalkyl, carbocycle, or heterocycle, or R^x and R^y, together with the atom to which they are attached, form a 3-8 membered carbocycle or heterocycle.

[0039] Described herein are compounds having the structure of Formula (I):

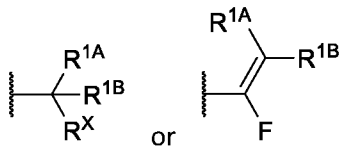


(I)

or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, or salt thereof, wherein:

A is N or CR^{2c};

R^1 is



wherein

R^x is F, O-R^{1C} or N(R^{1C})R^{1D};

R^{1A} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1B} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$

R^{1C} is H,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1D} is H,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$; or

R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring, optionally containing an O, N or S atom;

and wherein R^1 comprises at least one Fluorine atom;

R^{2a} is H, C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^{2b} is H, −CN, −C(O)OH, −C(O)OC_{1-4}alkyl, −C(O)NR^5R^6, or 5- or 6-membered heteroaryl, wherein R^{2b} is substituted with 0-2 R';

R^{2c} is H, halo, −CN, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4}haloalkyl;

R^3 is H, C_{2-4} alkoxy, −C(O)R^7, carbocycle, heterocycle, aryl or heteroaryl, wherein R^3 is substituted with 0-2 R';

R^5 is H or C_{1-4} alkyl;

R^6 is H, C_{1-4} alkyl, −$(CH_2)_m$−carbocycle, −$(CH_2)_m$−heterocycle, −$(CH_2)_m$−aryl or −$(CH_2)_m$−heteroaryl;

R^7 is C_{1-4} alkyl, −$(CH_2)_n$−OH, −$(CH_2)_n$−OC_{1-4}alkyl, −$(CH_2)_n$−NH_2, −$(CH_2)_n$−NHC_{1-4}alkyl, −$(CH_2)_n$−N(C_{1-4}alkyl)(C_{1-4}alkyl), −$(CH_2)_n$−carbocycle, −$(CH_2)_n$−heterocycle , −$(CH_2)_m$−aryl, −$(CH_2)_m$−heteroaryl or halocycloalkyl, wherein R^7 is substituted with 0-2 R';

R' is −CN, −NO_2, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, alkoxyalkyl, carbocycle, −$(CH_2)_q$−NRR, −$(CH_2)_q$−C(O)R, −$(CH_2)_q$−C(O)OR, −$(CH_2)_q$−C(O)NRR, −$(CH_2)_q$−NHC(O)R, −$(CH_2)_q$−$S(O)_2$R, -$(CH_2)_q$-carbocycle or -$(CH_2)_q$-heterocycle;

each R is, independently, H, C_{1-4} alkyl, carbocycle or heterocycle;

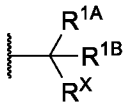
m is 0-2;

n is 0-2; and

q is 0-4.

[0040] Also described herein are compounds having the structure of Formula (I). In other embodiments, compounds are provided which are pharmaceutically acceptable salts of Formula (I). In other embodiments, compounds are provided which are solvates of Formula (I). In other embodiments, compounds are provided which are hydrates of Formula (I). In other embodiments, compounds are provided which are isomers of Formula (I). In other embodiments, compounds are provided which are tautomers of Formula (I). In other embodiments, compounds are provided which are racemates of Formula (I). In other embodiments, compounds are provided which are isotopes of Formula (I).

[0041] In some embodiments, R^1 is



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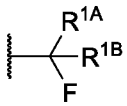
[0042] In some embodiments, R^1 is



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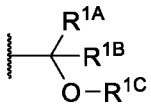
[0043] In some embodiments, R^1 is



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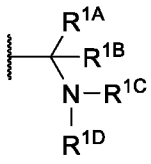
[0044] In some embodiments, R^1 is



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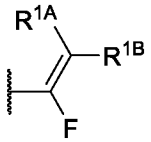
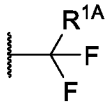
[0045] In some embodiments, R^1 is



[0046] In some embodiments, R^1 is



[0047] In some embodiments, R^{1A} is H. In other embodiments, R^{1A} is halogen. In other embodiments, R^{1A} is Cl or F. In other embodiments, R^{1A} is F. In other embodiments, R^{1A} is methyl, ethyl, propyl or butyl. In other embodiments, R^{1A} is -C_{1-4} haloalkyl.

[0048] In some embodiments, R^{1A} is -C_{1-4} haloalkyl containing 1 F atom. In other embodiments, R^{1A} is -C_{1-4} haloalkyl containing 2 F atoms. In other embodiments, R^{1A} is -C_{1-4} haloalkyl containing 3 F atoms. In other embodiments, R^{1A} is -C_{1-4} haloalkyl containing more than 3 F atoms.

[0049] In other embodiments, R^{1A} is cycloalkyl or heterocycloalkyl. In other embodiments, R^{1A} is halocycloalkyl. In other embodiments, R^{1A} is halocycloalkyl containing 1 F atom. In other embodiments, R^{1A} is halocycloalkyl containing 2 F atoms. In other embodiments, R^{1A} is halocycloalkyl containing 3 F atoms. In other embodiments, R^{1A} is halocycloalkyl containing more than 3 F atoms.

[0050] In some embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein n is 0. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein n is 1. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein n is 2. In other embodiments, R^{1A} is -$(CH_2)_n$NRR or -$(CH_2)_n$OR. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein R comprises at least one F atom. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein R comprises one F atom. In other embodiments, R^{1A} is -$(CH_2)_n$CN, -$(CH_2)_n$NRR, -$(CH_2)_n$OR, -$(CH_2)_n$C(=O)R, -$(CH_2)_n$C(=O)OR, -$(CH_2)_n$C(=O)NRR, wherein R comprises 2 F atoms. In other

embodiments, R^{1A} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 3 F atoms. In other embodiments, R^{1A} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises more than 3 F atoms.

[0051] In some embodiments, R^{1A} is heteroaryl. In other embodiments, R^{1A} is a 5-membered heteroaryl. In other embodiments, R^{1A} is a 6-membered heteroaryl. In other embodiments, R^{1A} is heteroaryl comprising one O or N atom.

[0052] In some embodiments, R^{1B} is H. In other embodiments, R^{1B} is halogen. In other embodiments, R^{1B} is Cl or F. In other embodiments, R^{1B} is F. In other embodiments, R^{1B} is methyl, ethyl, propyl or butyl. In other embodiments, R^{1B} is $-C_{1-4}$ haloalkyl.

[0053] In some embodiments, R^{1B} is $-C_{1-4}$ haloalkyl containing 1 F atom. In other embodiments, R^{1B} is $-C_{1-4}$ haloalkyl containing 2 F atoms. In other embodiments, R^{1B} is $-C_{1-4}$ haloalkyl containing 3 F atoms. In other embodiments, R^{1B} is $-C_{1-4}$ haloalkyl containing more than 3 F atoms.

[0054] In other embodiments, R^{1B} is cycloalkyl or heterocycloalkyl. In other embodiments, R^{1B} is halocycloalkyl. In other embodiments, R^{1B} is halocycloalkyl containing 1 F atom. In other embodiments, R^{1B} is halocycloalkyl containing 2 F atoms. In other embodiments, R^{1B} is halocycloalkyl containing 3 F atoms. In other embodiments, R^{1B} is halocycloalkyl containing more than 3 F atoms.

[0055] In some embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 0. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 1. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 2.

[0056] In other embodiments, R^{1B} is $-(CH_2)_nNRR$ or $-(CH_2)_nOR$. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises at least one F atom. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises one F atom. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$,

$-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 2 F atoms. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 3 F atoms. In other embodiments, R^{1B} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises more than 3 F atoms.

[0057] In some embodiments, R^{1B} is heteroaryl. In some embodiments, R^{1B} is a 5-membered heteroaryl. In some embodiments, R^{1B} is a 6-membered heteroaryl. In some embodiments, R^{1B} is heteroaryl comprising one O or N atom.

[0058] In some embodiments, R^{1C} is H. In other embodiments, R^{1C} is methyl, ethyl, propyl or butyl. In other embodiments, R^{1C} is $-C_{1-4}$ haloalkyl. In some embodiments, R^{1C} is $-C_{1-4}$ haloalkyl containing 1 F atom. In other embodiments, R^{1C} is $-C_{1-4}$ haloalkyl containing 2 F atoms. In other embodiments, R^{1C} is $-C_{1-4}$ haloalkyl containing 3 F atoms. In other embodiments, R^{1C} is $-C_{1-4}$ haloalkyl containing more than 3 F atoms.

[0059] In some embodiments, R^{1C} is cycloalkyl or heterocycloalkyl. In other embodiments, R^{1C} is halocycloalkyl. In other embodiments, R^{1C} is halocycloalkyl containing 1 F atom. In other embodiments, R^{1C} is halocycloalkyl containing 2 F atoms. In other embodiments, R^{1C} is halocycloalkyl containing 3 F atoms. In other embodiments, R^{1C} is halocycloalkyl containing more than 3 F atoms.

[0060] In some embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 0. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 1. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 2. In other embodiments, R^{1C} is $-(CH_2)_nNRR$ or $-(CH_2)_nOR$. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises at least one F atom. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises one F atom. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 2 F atoms. In other

embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 3 F atoms. In other embodiments, R^{1C} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises more than 3 F atoms.

[0061] In some embodiments, R^{1C} is heteroaryl. In some embodiments, R^{1C} is a 5-membered heteroaryl. In some embodiments, R^{1C} is a 6-membered heteroaryl. In some embodiments, R^{1C} is heteroaryl comprising one O or N atom.

[0062] In some embodiments, R^{1D} is H. In other embodiments, R^{1D} is methyl, ethyl, propyl or butyl. In other embodiments, R^{1D} is $-C_{1-4}$ haloalkyl. In some embodiments, R^{1D} is $-C_{1-4}$ haloalkyl containing 1 F atom. In other embodiments, R^{1D} is $-C_{1-4}$ haloalkyl containing 2 F atoms. In other embodiments, R^{1D} is $-C_{1-4}$ haloalkyl containing 3 F atoms. In other embodiments, R^{1D} is $-C_{1-4}$ haloalkyl containing more than 3 F atoms.

[0063] In other embodiments, R^{1D} is cycloalkyl or heterocycloalkyl. In other embodiments, R^{1D} is halocycloalkyl. In other embodiments, R^{1D} is halocycloalkyl containing 1 F atom. In other embodiments, R^{1D} is halocycloalkyl containing 2 F atoms. In other embodiments, R^{1D} is halocycloalkyl containing 3 F atoms. In other embodiments, R^{1D} is halocycloalkyl containing more than 3 F atoms.

[0064] In some embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 0. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 1. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein n is 2. In other embodiments, R^{1D} is $-(CH_2)_nNRR$ or $-(CH_2)_nOR$. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises at least one F atom. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises one F atom. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises 2 F atoms. In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$,

$-(CH_2)_nC(=O)NRR$, wherein R comprises 3 F atoms.In other embodiments, R^{1D} is $-(CH_2)_nCN$, $-(CH_2)_nNRR$, $-(CH_2)_nOR$, $-(CH_2)_nC(=O)R$, $-(CH_2)_nC(=O)OR$, $-(CH_2)_nC(=O)NRR$, wherein R comprises more than 3 F atoms.

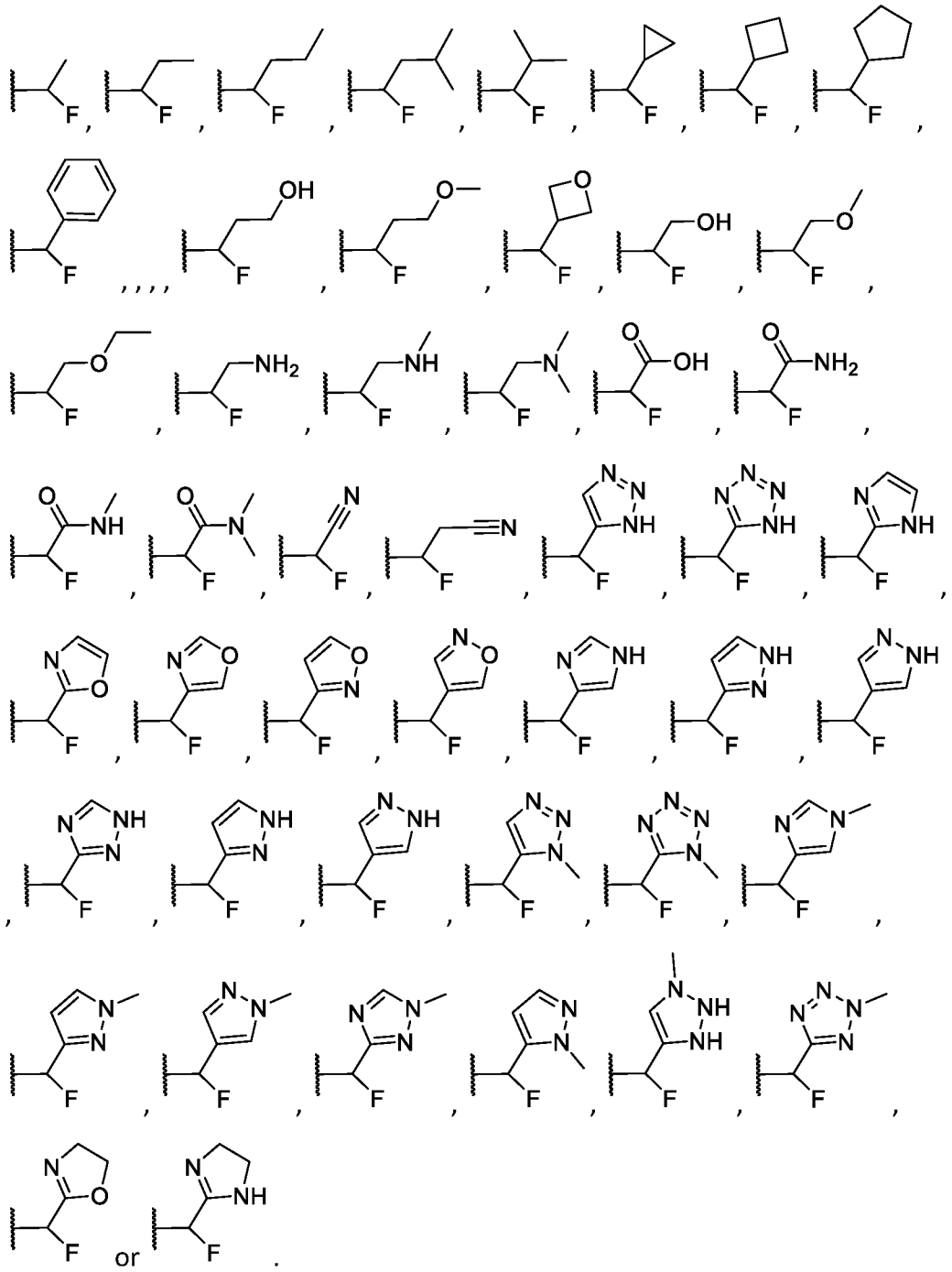
[0065] In some embodiments, R^{1D} is heteroaryl. In some embodiments, R^{1D} is a 5-membered heteroaryl. In some embodiments, R^{1D} is a 6-membered heteroaryl. In some embodiments, R^{1D} is heteroaryl comprising one O or N atom.

[0066] In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3-membered ring, optionally containing an O, N or S atom. In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 4- membered ring, optionally containing an O, N or S atom. In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 5- membered ring, optionally containing an O, N or S atom. In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 6- membered ring, optionally containing an O, N or S atom.

[0067] In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring, containing an O atom. In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring, containing an N atom. In some embodiments, R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring, containing a S atom.

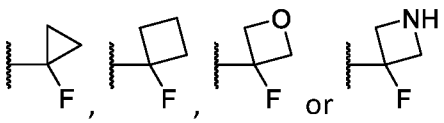
[0068] In some embodiments, R^1 comprises one Fluorine atom. In some embodiments, R^1 comprises two Fluorine atoms. In some embodiments, R^1 comprises three Fluorine atoms. In some embodiments, R^1 comprises more than three Fluorine atoms.

[0069] In some embodiments, R^1 is



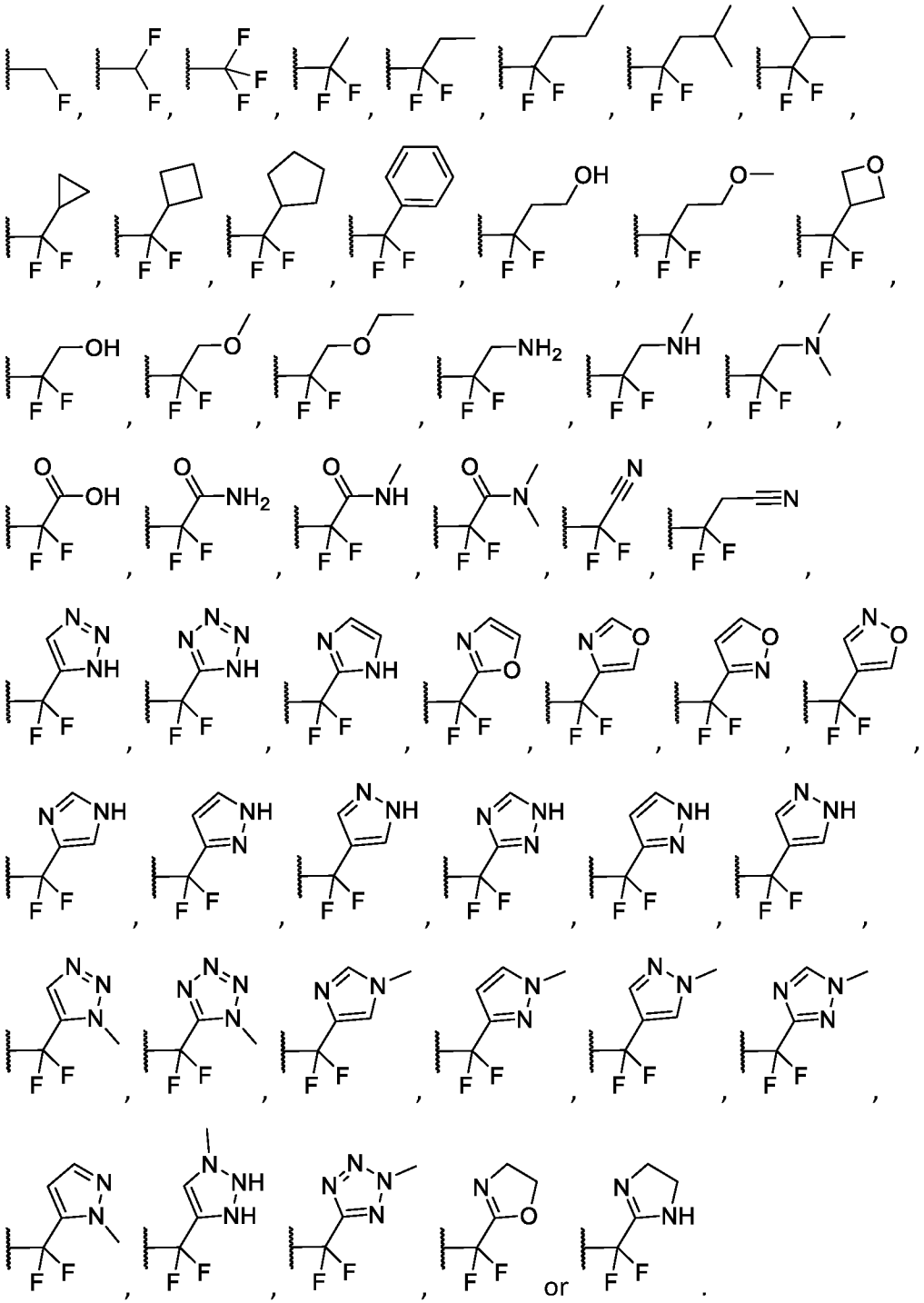
[0070] In some embodiments, R^X is F and R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring.

[0071] In some embodiments, R^1 is



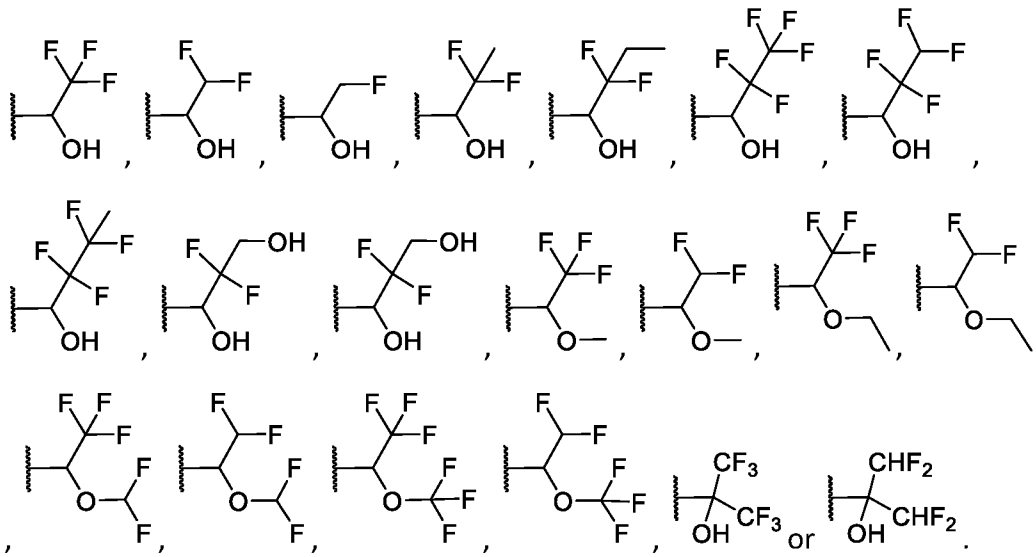
[0072] In some embodiments, R^X is F and R^{1A} is F.

[0073] In some embodiments, R^1 is



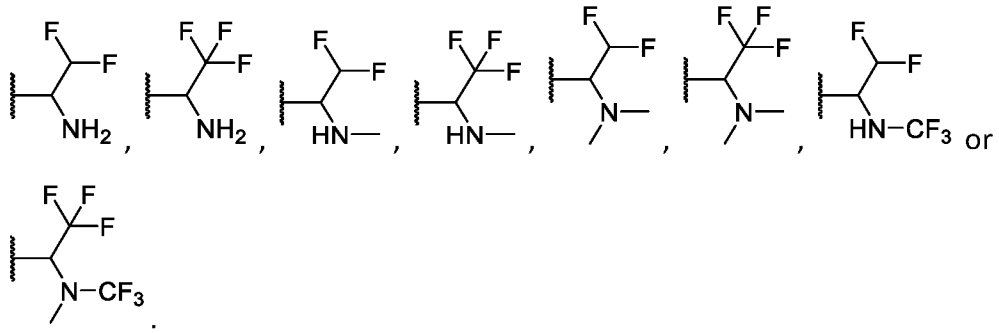
[0074] In some embodiments, R^X is O-R^{1C}. In other embodiments, R^X is OH or OMe.

[0075] In some embodiments, R^1 is

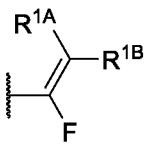


[0076] In some embodiments, R^X is $N(R^{1C})R^{1D}$. In some embodiments, R^X is NH_2, NHMe or NMe_2.

[0077] In some embodiments, R^1 is

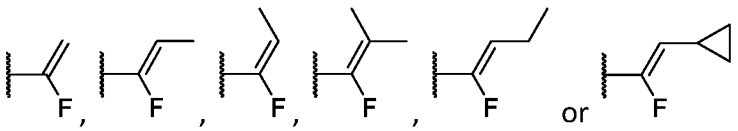


[0078] In some embodiments, R^1 is



[0079] In some embodiments, R^{1A} is H and R^{1B} is,-C_{1-4} alkyl or cycloalkyl.

[0080] In some embodiments, R^1 is



[0081] In some embodiments R^{2a} is H. In other embodiments R^{2a} is C_{1-4} alkyl. In other embodiments R^{2a} is C_{1-4} fluoroalkyl. In other embodiments R^{2a} is methyl. In other

embodiments R^{2a} is ethyl. In other embodiments R^{2a} is difluoromethyl. In other embodiments R^{2a} is trifluoromethyl. In other embodiments R^{2a} is fluoroethyl.

[0082] In some embodiments R^{2b} is H. In other embodiments R^{2b} is −CN. In other embodiments R^{2b} is R^{2b} is -C(O)OH or -C(O)OC_{1-4}alkyl. In other embodiments R^{2b} is −C(O)OH. In other embodiments R^{2b} is −C(O)OC_{1-4}alkyl. In other embodiments R^{2b} is −C(O)OMe. In other embodiments R^{2b} is −C(O)NR^5R^6. In other embodiments R^{2b} is −C(O)NH_2. In other embodiments R^{2b} is −C(O)NHR^6. In other embodiments R^{2b} is −C(O)NH-C_{1-4} alkyl. In other embodiments R^{2b} is −C(O)NHMe. In other embodiments R^{2b} is −C(O)NMe_2. In other embodiments R^{2b} is −C(O)NHEt. In other embodiments R^{2b} is -C(O)NH-CH_2-carbocycle, -C(O)NH-CH_2-heterocycle, -C(O)NH-CH_2-aryl or -C(O)NH-CH_2-heteroaryl. In other embodiments R^{2b} is -C(O)NH-CH_2-carbocycle, -C(O)NH-CH_2-heterocycle, -C(O)NH-CH_2-aryl or -C(O)NH-CH_2-heteroaryl, substituted with halo or C_{1-6} alkyl. In other embodiments R^{2b} is -C(O)NH-CH_2-heterocycle or -C(O)NH-CH_2-heteroaryl, substituted with F or methyl. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−carbocycle. In other embodiments R^{2b} is −C(O)NH−carbocycle. In other embodiments R^{2b} is −C(O)NH−(CH_2)−carbocycle. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_2$−carbocycle. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−heterocycle. In other embodiments R^{2b} is −C(O)NH−heterocycle. In other embodiments R^{2b} is −C(O)NH−(CH_2)−heterocycle. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_2$−heterocycle. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−aryl. In other embodiments R^{2b} is −C(O)NH−aryl. In other embodiments R^{2b} is −C(O)NH−aryl substituted with 1 or 2 R′. In other embodiments R^{2b} is −C(O)NH−phenyl.

[0083] In other embodiments R^{2b} is −C(O)NH−phenyl substituted with 1 R′. In other embodiments R^{2b} is −C(O)NH−phenyl substituted with 2 R′. In other embodiments R^{2b} is −C(O)NH−(CH_2)−aryl. In other embodiments R^{2b} is −C(O)NH−(CH_2)−aryl substituted with 1 or 2 R′. In other embodiments R^{2b} is −C(O)NH−(CH_2)−aryl substituted with 1 R′. In other embodiments R^{2b} is −C(O)NH−(CH_2)−aryl substituted with 2 R′. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_2$−aryl. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−heteroaryl. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−heteroaryl substituted with 1 or 2 R′. In other embodiments R^{2b} is −C(O)NH−$(CH_2)_m$−heteroaryl

substituted with 1 R'. In other embodiments R^{2b} is $-C(O)NH-(CH_2)_m-$heteroaryl substituted with 2 R'. In other embodiments R^{2b} is $-C(O)NH-$heteroaryl. In other embodiments R^{2b} is $-C(O)NH-(CH_2)-$heteroaryl. In other embodiments R^{2b} is $-C(O)NH-(CH_2)_2-$heteroaryl.

[0084] In some embodiments R^{2b} is 5- or 6-membered heteroaryl, substituted with 0-2 R'. In other embodiments R^{2b} is a 5- or 6-membered heteroaryl. In other embodiments R^{2b} is a 5-membered heteroaryl. In other embodiments R^{2b} is a 6-membered heteroaryl. In other embodiments R^{2b} is a 5- or 6-membered heteroaryl substituted with 0-2 R'. In other embodiments R^{2b} is 5- or 6-membered heteroaryl, substituted with methyl. In other embodiments R^{2b} is 5membered heteroaryl, substituted with methyl. In other embodiments R^{2b} is 6-membered heteroaryl, substituted with methyl. In other embodiments R^{2b} is a 5-membered heteroaryl substituted with 0-2 R'. In other embodiments R^{2b} is a 6-membered heteroaryl substituted with 0-2 R'. In other embodiments R^{2b} is a. 5- or 6-membered heteroaryl substituted with 1 R'. In other embodiments R^{2b} is a. 5-membered heteroaryl substituted with 1 R'. In other embodiments R^{2b} is a. 6-membered heteroaryl substituted with 1 R'. In other embodiments R^{2b} is a. 5- or 6-membered heteroaryl substituted with 2 R'. In other embodiments R^{2b} is a. 5-membered heteroaryl substituted with 2 R'. In other embodiments R^{2b} is a. 6-membered heteroaryl substituted with 2 R'.

[0085] In some embodiments R^{2c} is H. In other embodiments R^{2c} is halo. In other embodiments R^{2c} is Cl. In other embodiments R^{2c} is F. In other embodiments R^{2c} is $-CN$. In other embodiments R^{2c} is C_{1-4} alkyl. In other embodiments R^{2c} is Me. In other embodiments R^{2c} is Et.

[0086] In other embodiments R^{2c} is C_{1-4} alkoxy. In other embodiments R^{2c} is OMe. In other embodiments R^{2c} is OEt. In other embodiments R^{2c} is C_{1-4}haloalkyl. In some embodiments R^3 is H.In other embodiments R^{2c} is CF_3.

[0087] In some embodiments R^3 is H. In other embodiments R^3 is C_{2-4} alkoxy. In other embodiments R^3 is OMe. In other embodiments R^3 isOEt. In other embodiments R^3 is carbocycle, heterocycle, aryl or heteroaryl. In other embodiments R^3 is carbocycle, heterocycle, aryl or heteroaryl, substituted with 1 or 2 R'. In other embodiments R^3 is

carbocycle, heterocycle, aryl or heteroaryl, substituted with 1 R′. In other embodiments R^3 is carbocycle, heterocycle, aryl or heteroaryl, substituted with 2 R′. In other embodiments R^3 is aryl or heteroaryl substituted with 1 or 2 R'. In other embodiments R^3 is aryl or heteroaryl substituted with 1 R'. In other embodiments R^3 is aryl or heteroaryl substituted with 2 R'. In other embodiments R^3 is carbocycle. In other embodiments R^3 is carbocycle, substituted with 1 or 2 R'. In other embodiments R^3 is carbocycle, substituted with 1 R′. In other embodiments R^3 is heterocycle. In other embodiments R^3 is heterocycle, substituted with 1 or 2 R'.In other embodiments R^3 is heterocycle, substituted with 1 R′.In other embodiments R^3 is aryl. In other embodiments R^3 is aryl, substituted with 1 or 2 R'.In other embodiments R^3 is aryl, substituted with 1 R′. In other embodiments R^3 is phenyl. In other embodiments R^3 is phenyl, substituted with 1 or 2 R'. In other embodiments R^3 is phenyl, substituted with 1 R′. In other embodiments R^3 is heteroaryl. In other embodiments R^3 is heteroaryl, substituted with 1 or 2 R'. In other embodiments R^3 is heteroaryl, substituted with 1 R′. In other embodiments R^3 is pyridyl. In other embodiments R^3 is pyridyl, substituted with 1 or 2 R'. In other embodiments R^3 is pyridyl, substituted with 1 R′.

[0088] In some embodiments R^3 is $-C(O)R^7$. In some embodiments R^7 is $-(CH_2)_n-$carbocycle, $-(CH_2)_n-$heterocycle, $-(CH_2)_m-$aryl or $-(CH_2)_m-$heteroaryl. In some embodiments R^7 is $-(CH_2)_n-$carbocycle, $-(CH_2)_n-$heterocycle, $-(CH_2)_m-$aryl or $-(CH_2)_m-$heteroaryl, substituted with 1 or 2 R'. In some embodiments R^7 is $-(CH_2)_n-$carbocycle, $-(CH_2)_n-$heterocycle, $-(CH_2)_m-$aryl or $-(CH_2)_m-$heteroaryl, substituted with 1 R'. In other embodiments R^7 is C_{1-4} alkyl or carbocycle. In other embodiments R^7 is C_{1-4} alkyl or carbocycle, substituted with 1 or 2 R'. In other embodiments R^7 is C_{1-4} alkyl or carbocycle, substituted with 1 R'. In other embodiments R^7 is carbocycle, heterocycle, aryl or heteroaryl. In other embodiments R^7 is carbocycle, heterocycle, aryl or heteroaryl, substituted with 1 or 2 R'. In other embodiments R^7 is carbocycle, heterocycle, aryl or heteroaryl, substituted with 1 R'.

[0089] In other embodiments R^3 is $-C(O)$ C_{1-4} alkyl. In other embodiments R^3 is $-C(O)Me$.

[0090] In other embodiments R^3 is −C(O)Et. In other embodiments R^3 is −C(O)-halocycloalkyl. In other embodiments R^3 is $-C(O)-(CH_2)_n-OH$. In other embodiments R^3 is −C(O)OH. In other embodiments R^3 is $-C(O)-(CH_2)-OH$. In other embodiments R^3 is $-C(O)-(CH_2)_2-OH$.

[0091] In other embodiments R^3 is $-C(O)-(CH_2)_n-OC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-OC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)-OC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)_2-OC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)_n-OMe$. In other embodiments R^3 is −C(O)−OMe. In other embodiments R^3 is $-C(O)-(CH_2)-OMe$. In other embodiments R^3 is $-C(O)-(CH_2)_2-OMe$. In other embodiments R^3 is $-C(O)-(CH_2)_n-NH_2$. In other embodiments R^3 is $-C(O)-NH_2$. In other embodiments R^3 is $-C(O)-(CH_2)-NH_2$. In other embodiments R^3 is $-C(O)-(CH_2)_2-NH_2$. In other embodiments R^3 is $-C(O)-(CH_2)_n-NHC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-NHC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)-NHC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)_2-NHC_{1-4}$alkyl. In other embodiments R^3 is $-C(O)-(CH_2)_n-NHMe$. In other embodiments R^3 is −C(O)−NHMe. In other embodiments R^3 is $-C(O)-(CH_2)-NHMe$. In other embodiments R^3 is $-C(O)-(CH_2)_2-NHMe$. In other embodiments R^3 is $-C(O)-(CH_2)_n-N(C_{1-4}alkyl)(C_{1-4}alkyl)$. In other embodiments R^3 is $-C(O)-N(C_{1-4}alkyl)(C_{1-4}alkyl)$. In other embodiments R^3 is $-C(O)-(CH_2)-N(C_{1-4}alkyl)(C_{1-4}alkyl)$. In other embodiments R^3 is $-C(O)-(CH_2)_2-N(C_{1-4}alkyl)(C_{1-4}alkyl)$. In other embodiments R^3 is $-C(O)-(CH_2)_n-NMe_2$. In other embodiments R^3 is $-C(O)-NMe_2$. In other embodiments R^3 is $-C(O)-(CH_2)-NMe_2$. In other embodiments R^3 is $-C(O)-(CH_2)_2-NMe_2$. In other embodiments R^3 is $-C(O)-(CH_2)_n-$carbocycle. In other embodiments R^3 is −C(O)−carbocycle. In other embodiments R^3 is $-C(O)-(CH_2)-$carbocycle. In other embodiments R^3 is $-C(O)-(CH_22-$carbocycle. In other embodiments R^3 is $-C(O)-(CH_2)_n-$heterocycle. In other embodiments R^3 is −C(O)−heterocycle. In other embodiments R^3 is $-C(O)-(CH_2)-$heterocycle. In other embodiments R^3 is $-C(O)-(CH_2)_2-$heterocycle. In other embodiments R^3 is $-C(O)-(CH_2)_m-$aryl. In other embodiments R^3 is −C(O)−aryl. In other embodiments R^3 is $-C(O)-(CH_2)-$aryl. In other embodiments R^3 is $-C(O)-(CH_2)_2-$aryl. In other embodiments R^3 is $-C(O)-(CH_2)_m-$heteroaryl. In other embodiments R^3 is

−C(O)−heteroaryl. In other embodiments R^3 is −C(O)−(CH_2)−heteroaryl. In other embodiments R^3 is −C(O)−$(CH_2)_2$−heteroaryl.

[0092] In other embodiments R^7 is substituted with 1 or 2 R'. In other embodiments R^7 is unsubstituted. In other embodiments R^7 is substituted with 1 R'. In other embodiments R^7 is substituted with 2 R'. In other embodiments m is 0, 1 or 2. In other embodiments m is 0. In other embodiments m is 1. In other embodiments m is 2. In other embodiments n is 0, 1 or 2. In other embodiments n is 0. In other embodiments n is 1. In other embodiments n is 2.

[0093] In some embodiments R' is halo. In other embodiments R' is Cl. In other embodiments R' is F. In other embodiments R' is $C_{1\text{-}6}$ alkyl. In other embodiments R' is Me. In other embodiments R' is Et. In other embodiments R' is $C_{1\text{-}6}$ alkoxy. In other embodiments R' is -OMe. In other embodiments R' is -OEt. In other embodiments R' is -CN. In other embodiments R' is $-NO_2$. In other embodiments R' is $C_{1\text{-}6}$ haloalkyl. In other embodiments R' is CF_3. In other embodiments R' is $C_{1\text{-}6}$ hydroxyalkyl. In other embodiments R' is CH_2OH. In other embodiments R' is $C_{1\text{-}6}$ alkoxy. In other embodiments R' is OMe. In other embodiments R' is $C_{1\text{-}6}$ haloalkoxy. In other embodiments R' is OCF_3. In other embodiments R' is alkoxyalkyl. In other embodiments R' is CH_2OMe. In other embodiments R' is a carbocycle. In other embodiments R' is a heterocycle. In other embodiments R' is $-(CH_2)_q-N(R)_2$. In other embodiments R' is $-(CH_2)_q-NH_2$. In other embodiments R' is $-(CH_2)_q$−NHMe.In other embodiments R' is $-(CH_2)_q-NMe_2$. In other embodiments R' is $-(CH_2)_q$−NH- carbocycle. In other embodiments R' is $-(CH_2)_q$−NH- heterocycle.

[0094] In other embodiments R' is $-N(R)_2$. In other embodiments R' is $-NH_2$. In other embodiments R' is $-NMe_2$. In other embodiments R' is −NHMe. In other embodiments R' is −NH-carbocycle.In other embodiments R' is −NH-heterocycle. In other embodiments R' is $-(CH_2)_q-C(O)R$. In other embodiments R' is $-(CH_2)_q-C(O)H$. In other embodiments R' is $-(CH_2)_q-C(O)Me$. In other embodiments R' is $-(CH_2)_q$−C(O)-carbocycle. In other embodiments R' is $-(CH_2)_q$−C(O)-heterocycle. In other embodiments R' is −C(O)R. In other embodiments R' is −C(O)H. In other embodiments R' is −C(O)Me. In other embodiments R' is −C(O)-carbocycle. In other embodiments R'

is −C(O)-heterocycle. In other embodiments R' is $-(CH_2)_q-C(O)OR$. In other embodiments R' is $-(CH_2)_q-C(O)OH$. In other embodiments R' is $-(CH_2)_q-C(O)OMe$. In other embodiments R' is $-(CH_2)_q-C(O)O$-carbocycle. In other embodiments R' is $-(CH_2)_q-C(O)O$-heterocycle. In other embodiments R' is −C(O)OR. In other embodiments R' is −C(O)OH. In other embodiments R' is −C(O)OMe. In other embodiments R' is −C(O)O-carbocycle. In other embodiments R' is −C(O)O-heterocycle. In other embodiments R' is $-(CH_2)_q-C(O)N(R)_2$. In other embodiments R' is $-(CH_2)_q-C(O)NH_2$. In other embodiments R' is $-(CH_2)_q-C(O)NMe_2$. In other embodiments R' is $-(CH_2)_q-C(O)NHMe$. In other embodiments R' is $-(CH_2)_q-C(O)NH$-carbocycle. In other embodiments R' is $-(CH_2)_q-C(O)NH$-heterocycle. In other embodiments R' is $-C(O)N(R)_2$. In other embodiments R' is $-C(O)NH_2$. In other embodiments R' is $-C(O)NMe_2$. In other embodiments R' is −C(O)NHMe. In other embodiments R' is −C(O)NH-carbocycle. In other embodiments R' is −C(O)NH-heterocycle. In other embodiments R' is $-(CH_2)_q-NHC(O)R$. In other embodiments R' is $-(CH_2)_q-NHC(O)H$. In other embodiments R' is $-(CH_2)_q-NHC(O)Me$.

[0095] In other embodiments R' is −NHC(O)R. In other embodiments R' is −NHC(O)H. In other embodiments R' is −NHC(O)Me. In other embodiments R' is $-(CH_2)_q-S(O)_2R$. In other embodiments R' is $-(CH_2)_q-S(O)_2H$. In other embodiments R' is $-(CH_2)_q-S(O)_2Me$.

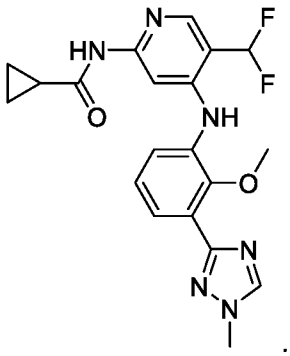
[0096] In other embodiments R' is $-S(O)_2R$. In other embodiments R' is $-S(O)_2H$. In other embodiments R' is $-S(O)_2Me$.

[0097] In some embodiments R' is a carbocycle. In other embodiments R' is $-(CH_2)_q-$heterocycle. In other embodiments R' is a heterocycle. In other embodiments R' is $-(CH_2)-$heterocycle. In other embodiments R' is $-(CH_2)_2-$heterocycle.

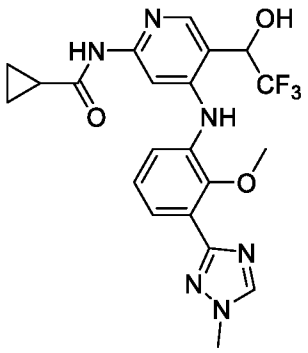
[0098] In some embodiments are compounds having a structure listed in Table 1, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof..In some embodiments, the compound has a structure listed in Table 1. In other embodiments, the compound is an isomer of a structure listed in Table 1. In other embodiments, the compound is a racemate of a structure listed in Table 1. In other embodiments, the compound is a hydrate of a structure listed in Table 1. In other embodiments, the compound is a solvate of a structure listed in Table 1. In other

embodiments, the compound is an isotope of a structure listed in Table 1. In other embodiments, the compound is a pharmaceutically acceptable salt of a structure listed in Table 1.

[0099] In some embodiments is a compound which is N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide



[0100] In some embodiments is a compound which is N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclopropanecarboxamide



[0101] In some embodiments are pharmaceutical compositions comprising a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments are pharmaceutical compositions comprising a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle.

[0102] In some embodiments are methods of treating diseases, comprising administering to a patient in need thereof, a therapeutically effective amount of a

compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

[0103] In some embodiments are methods of treating diseases, comprising administering to a patient suffering from the disease, a therapeutically effective amount of a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments are methods of treating a disease responsive to the inhibition of TYK2 kinase activity, comprising administering to a patient suffering from the disease, a therapeutically effective amount of a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments the disease is an inflammatory disease. In some embodiments the disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

[0104] In some embodiments are methods of treating diseases, comprising administering to a patient suffering from the disease, a therapeutically effective amount of a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent.

[0105] In some embodiments are kits, comprising a compound of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, and instructions for use.

[0106] In some embodiments are compounds of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, for use in treating an inflammatory disease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

[0107] In some embodiments are uses of compounds of formula (I), or an isomer, a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable

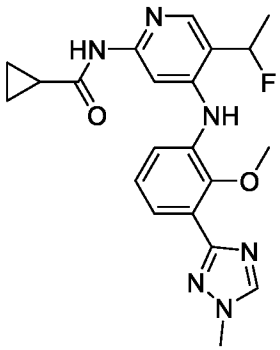
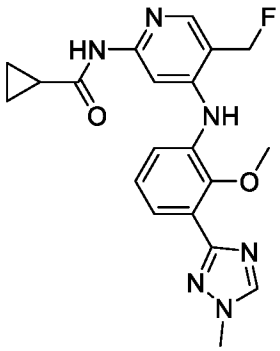
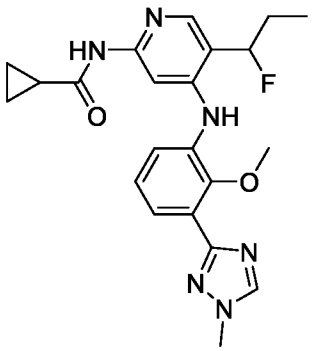
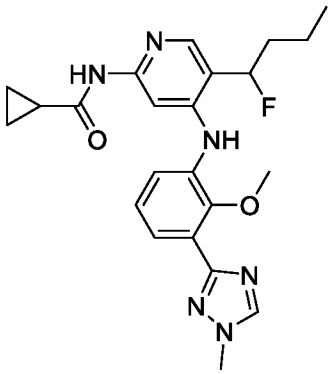
salt thereof, in the manufacture of a medicament for the treatment of an inflammatory disease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

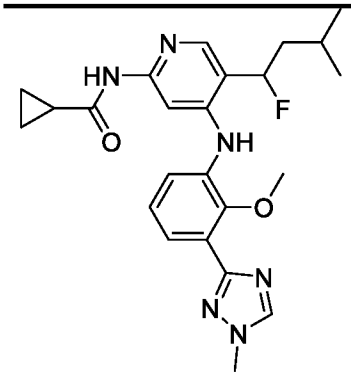
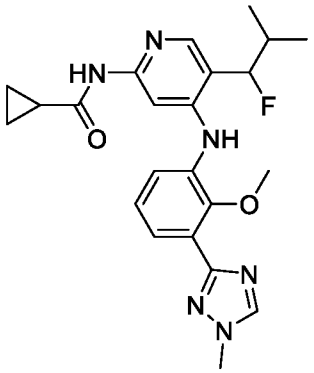
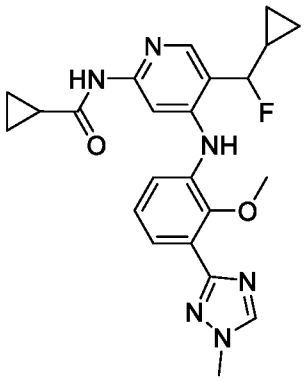
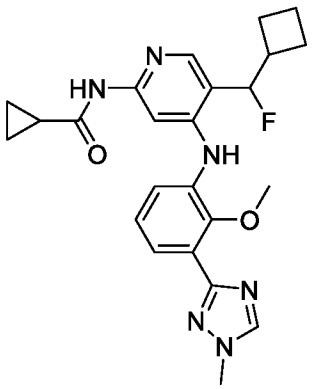
[0108] Also described herein are pharmaceutical compositions comprising compounds having the structure of Formula (I) or pharmaceutically acceptable salts, solvates, hydrates, isomers, tautomers, racemates, or isotopes thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical compositions comprise compounds having the structure of Formula (I), or pharmaceutically acceptable salts, solvates, hydrates, isomers, tautomers, racemates, or isotopes thereof, and at least one pharmaceutically acceptable excipient.

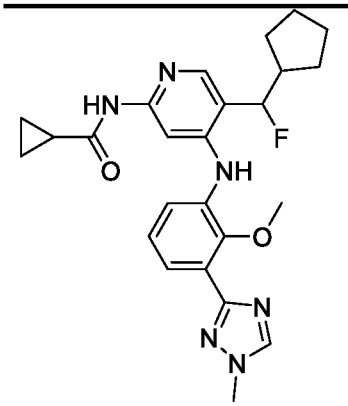
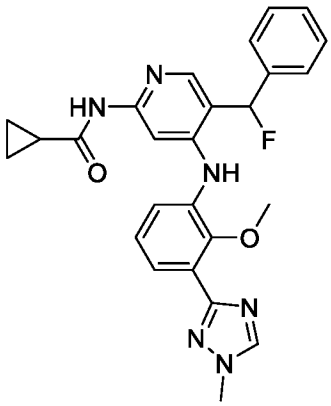
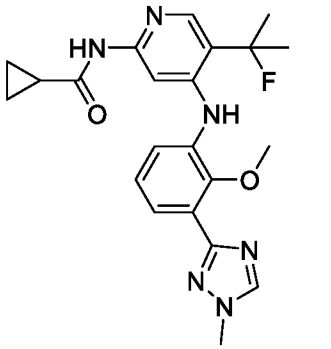
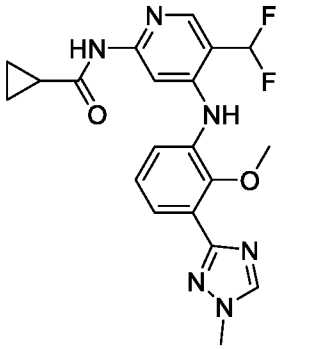
[0109] Also described herein are uses of compounds of Formula (I) or a pharmaceutically acceptable salts, solvates, hydrates, isomers, tautomers, racemates or isotopes thereof, in the manufacture of a medicament. In some embodiments the medicament is for the treatment of asthma. In some embodiments the medicament is for the treatment of inflammatory bowel disease. In some embodiments the medicament is for the treatment of Crohn's disease. In some embodiments the medicament is for the treatment of ulcerative colitis. In some embodiments the medicament is for the treatment of rheumatoid arthritis. In some embodiments the medicament is for the treatment of psoriasis. In some embodiments the medicament is for the treatment of allergic rhinitis. In some embodiments the medicament is for the treatment of atopic dermatitis. In some embodiments the medicament is for the treatment of contact dermatitis. In some embodiments the medicament is for the treatment of delayed hypersensitivity reactions. In some embodiments the medicament is for the treatment of lupus. In some embodiments the medicament is for the treatment of multiple sclerosis.

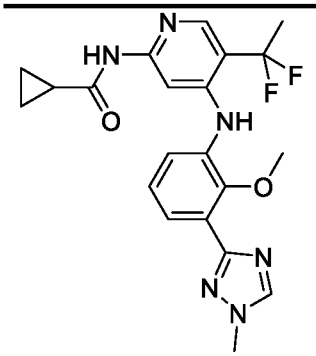
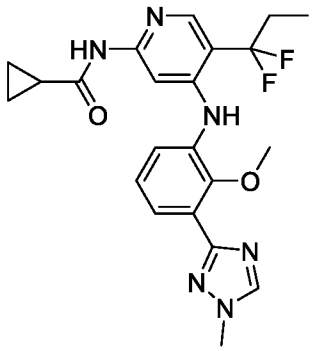
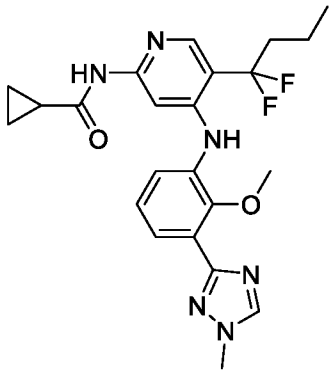
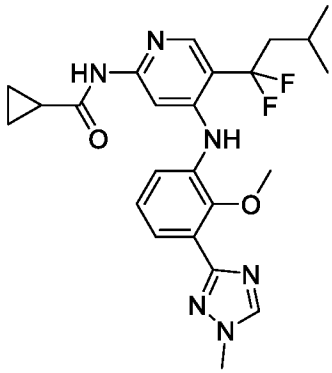
[0110] Representative compounds having the structure of Formula (I), as applicable, include the compounds listed in table 1, as well as pharmaceutically acceptable isomers, racemates, hydrates, solvates, isotopes, or salts thereof.

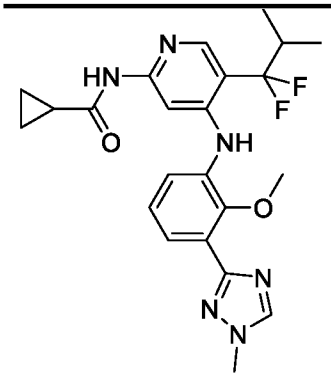
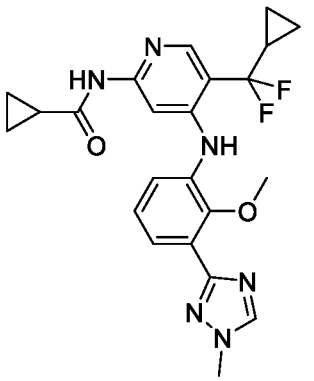
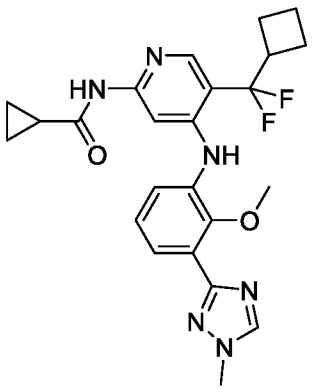
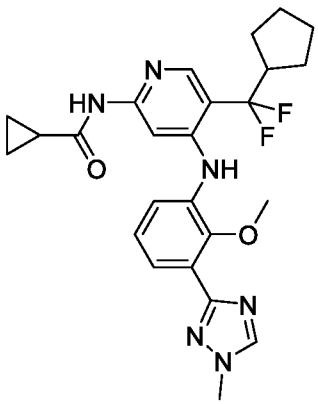
Table 1: Representative compounds

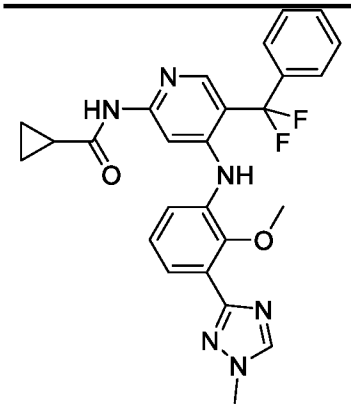
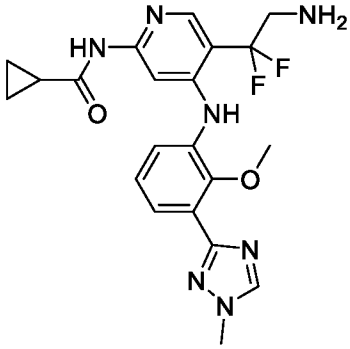
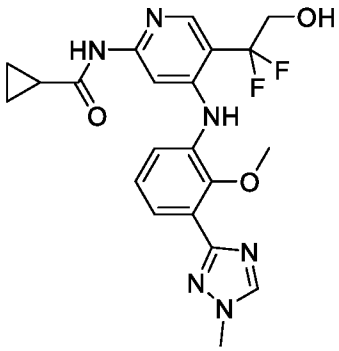
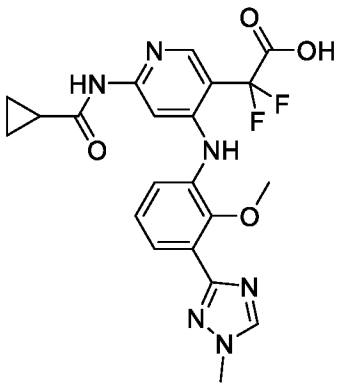
Structure	Name
	N-(5-(1-fluoroethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(fluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1-fluoropropyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1-fluorobutyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

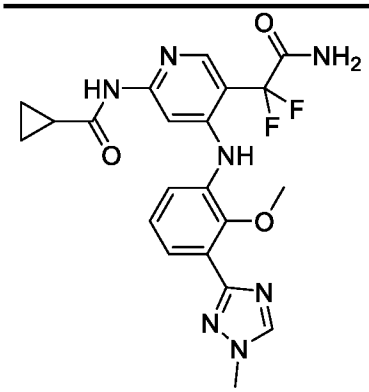
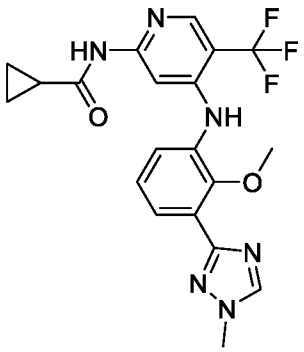
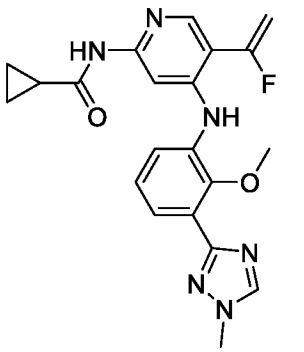
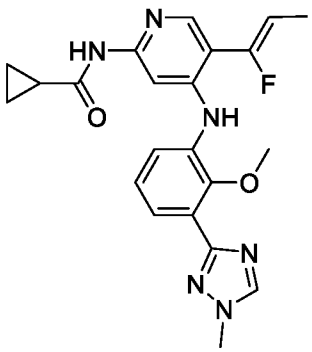
Structure	Name
	N-(5-(1-fluoro-3-methylbutyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1-fluoro-2-methylpropyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(cyclopropylfluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(cyclobutylfluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

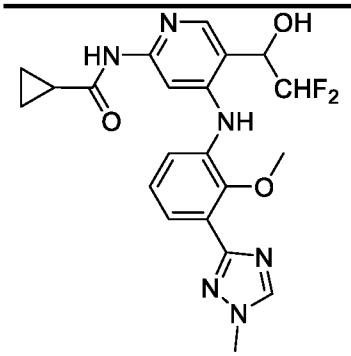
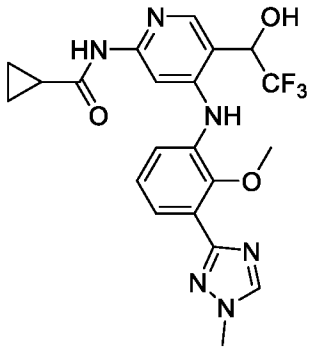
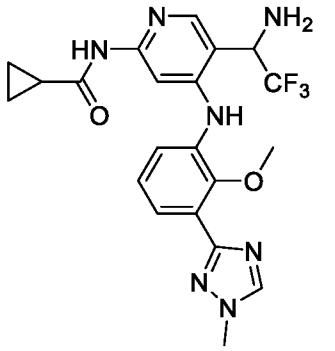
Structure	Name
	N-(5-(cyclopentylfluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(fluoro(phenyl)methyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(2-fluoropropan-2-yl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

Structure	Name
	N-(5-(1,1-difluoroethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1,1-difluoropropyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1,1-difluorobutyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1,1-difluoro-3-methylbutyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

Structure	Name
	N-(5-(1,1-difluoro-2-methylpropyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(cyclopropyldifluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(cyclobutyldifluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(cyclopentyldifluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

Structure	Name
	N-(5-(difluoro(phenyl)methyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(2-amino-1,1-difluoroethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	2-(6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-3-yl)-2,2-difluoroacetic acid
	2-(6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-3-yl)-2,2-difluoroacetic acid

Structure	Name
	N-(5-(2-amino-1,1-difluoro-2-oxoethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(trifluoromethyl)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1-fluorovinyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	(Z)-N-(5-(1-fluoroprop-1-en-1-yl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

Structure	Name
	N-(5-(2,2-difluoro-1-hydroxy-2l3-ethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide
	N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclopropanecarboxamide
	N-(5-(1-amino-2,2,2-trifluoroethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

[0111] "Isomer" as used herein to encompasses all chiral, diastereomeric or racemic forms of a structure, unless a particular stereochemistry or isomeric form is specifically indicated. Such compounds can be enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of certain embodiments of the disclosure. The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called "enantiomers." Single enantiomers

of a pure compound are optically active (i.e., they are capable of rotating the plane of plane polarized light and designated R or S).

[0112] "Isolated optical isomer" means a compound which has been substantially purified from the corresponding optical isomer(s) of the same Formula. For example, the isolated isomer may be at least about 80%, at least 80% or at least 85% pure. In other embodiments, the isolated isomer is at least 90% pure or at least 98% pure, or at least 99% pure by weight.

[0113] "Substantially enantiomerically or diastereomerically" pure means a level of enantiomeric or diastereomeric enrichment of one enantiomer with respect to the other enantiomer or diastereomer of at least about 80%, and more specifically in excess of 80%, 85%, 90%, 95%, 98%, 99%, 99.5% or 99.9%.

[0114] As used herein the terms "racemate" and "racemic mixture" refer to an equal mixture of two enantiomers. A racemate is labeled "(±)" because it is not optically active (i.e., will not rotate plane-polarized light in either direction since its constituent enantiomers cancel each other out).

[0115] Unless stated to the contrary, a Formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer, diastereomer, and meso compound, and a mixture of isomers, such as a racemic or scalemic mixture.

[0116] A "hydrate" is a compound that exists in combination with water molecules. The combination can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form; that is, a compound in a water solution, while it may be hydrated, is not a hydrate as the term is used herein.

[0117] A "solvate" is similar to a hydrate except that a solvent other that water is present. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometric or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form; that is, a compound in a solvent solution, while it may be solvated, is not a solvate as the term is used herein.

[0118] "Isotope" refers to atoms with the same number of protons but a different number of neutrons, and an isotope of a compound having the structure of Formula (I) includes any such compound wherein one or more atoms are replaced by an isotope of that atom. For example, carbon 12, the most common form of carbon, has six protons and six neutrons, whereas carbon 13 has six protons and seven neutrons, and carbon 14 has six protons and eight neutrons. Hydrogen has two stable isotopes, deuterium (one proton and one neutron) and tritium (one proton and two neutrons). While fluorine has a number of isotopes, fluorine 19 is longest-lived. Thus, an isotope of a compound having the structure of Formula (I) includes, but is not limited to, compounds having the structure of Formula wherein one or more carbon 12 atoms are replaced by carbon-13 and/or carbon-14 atoms, wherein one or more hydrogen atoms are replaced with deuterium and/or tritium, and/or wherein one or more fluorine atoms are replaced by fluorine-19.

[0119] "Salt" generally refers to an organic compound, such as a carboxylic acid or an amine, in ionic form, in combination with a counter ion. For example, salts formed between acids in their anionic form and cations are referred to as "acid addition salts". Conversely, salts formed between bases in the cationic form and anions are referred to as "base addition salts."

[0120] The term "pharmaceutically acceptable" refers an agent that has been approved for human consumption and is generally non-toxic. For example, the term "pharmaceutically acceptable salt" refers to nontoxic inorganic or organic acid and/or base addition salts (see, e.g., Lit et al., Salt Selection for Basic Drugs, Int. J. Pharm., 33, 201-217, 1986) (incorporated by reference herein).

Pharmaceutically acceptable base addition salts of compounds of the disclosure include, for example, metallic salts including alkali metal, alkaline earth metal, and transition metal salts such as, for example, calcium, magnesium, potassium, sodium, and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, N,N'dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine.

Pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, aromatic aliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids, examples of which include formic, acetic, trifluoroacetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, hippuric, malonic, oxalic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, panthothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, βhydroxybutyric, salicylic, -galactaric, and galacturonic acid.

[0121] Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of compounds having the structure of Formula (I), for example in their purification by recrystallization.

[0122] In certain embodiments, the disclosure provides a pharmaceutical composition comprising a compound having the structure of Formula (I), or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof, together with at least one pharmaceutically acceptable carrier, diluent, or excipient. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, or lower alkyl ethers of

cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose, and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

[0123] As used herein, the term "pharmaceutical composition" refers to a composition containing one or more of the compounds described herein, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, homolog or salt thereof, formulated with a pharmaceutically acceptable carrier, which can also include other additives, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gel cap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other formulation described herein. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005) and in The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013.

[0124] In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the disclosure with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the methods can further include the step of formulating the composition into a tablet or capsule. In other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In some such embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation.

[0125] As used herein, the term "pharmaceutically acceptable carrier" refers to any ingredient other than the disclosed compounds, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, homolog or salt thereof (e.g., a carrier capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: anti-adherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0126] The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances, preserving agents, sweetening agents, or flavoring agents. The compositions can also be sterilized if desired.

[0127] The route of administration can be any route which effectively transports the active compound of the disclosure to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, or parenteral, e.g., rectal, depot, subcutaneous, intravenous, inhalation of a dry powder form or a nebulized form, intraurethral, intramuscular, intranasal, ophthalmic solution, or an ointment, the oral route being preferred.

[0128] Dosage forms can be administered once a day, or more than once a day, such as twice or thrice daily. Alternatively, dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician. Dosing regimens include, for example, dose titration to the extent necessary or useful for the indication to be treated, thus allowing the patient's body to adapt to the treatment and/or to minimize or avoid unwanted side effects associated with the treatment. Other dosage forms include delayed or controlled-release forms. Suitable dosage regimens and/or forms include those set out, for example, in the latest edition of the Physicians' Desk Reference, incorporated herein by reference.

[0129] As used herein, the term "administering" or "administration" refers to providing a compound, a pharmaceutical composition comprising the same, to a subject by any acceptable means or route, including (for example) by oral, parenteral (e.g., intravenous), inhaled, or topical administration.

[0130] As used herein, the term "treatment" refers to an intervention that ameliorates a sign or symptom of a disease or pathological condition. As used herein, the terms "treatment", "treat" and "treating," with reference to a disease, pathological condition or symptom, also refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, a reduction in the number of relapses of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. A prophylactic treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs, for the purpose of decreasing the risk of developing pathology. A therapeutic treatment is a treatment administered to a subject after signs and symptoms of the disease have developed.

[0131] As used herein, the term "subject" refers to an animal (e.g., a mammal, such as a human). A subject to be treated according to the methods described herein may be

one who has been diagnosed with a disease, e.g., a subject diagnosed with an inflammatory disease or lupus, or one at risk of developing the condition. Diagnosis may be performed by any method or technique known in the art. One skilled in the art will understand that a subject to be treated according to the present disclosure may have been subjected to standard tests or may have been identified, without examination, as one at risk due to the presence of one or more risk factors associated with the disease or condition.

[0132] As used herein, the term "effective amount" refers to a quantity of a specified agent sufficient to achieve a desired effect in a subject being treated with that agent. Ideally, an effective amount of an agent is an amount sufficient to inhibit or treat the disease without causing substantial toxicity in the subject. The effective amount of an agent will be dependent on the subject being treated, the severity of the affliction, and the manner of administration of the pharmaceutical composition. Methods of determining an effective amount of the disclosed compound sufficient to achieve a desired effect in a subject will be understood by those of skill in the art in light of this disclosure.

[0133] As used herein, the term "therapeutically effective amount" is intended to include an amount of a compound of Formula (I) that is effective when administered alone or in combination to inhibit IL-23, IL-12 and/or IFNα function and/or treat diseases. The methods of treating IL-23-, IL-12 and/or IFNα-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit IL-23, IL-12 and/or IFNα function and/or treat diseases associated with IL-23, IL-12 and/or IFNα.

[0134] As used herein, the term "chemotherapeutic agent" includes any other pharmaceutically active compound that can be used in conjunction with the disclosed TYK2 inhibitors.

[0135] As used herein, the terms "IL-23-, IL-12- and/or IFNα-associated condition" or "IL-23-, IL-12- and/or IFNα-associated disease or disorder" are intended to encompass all of the

conditions identified above as if repeated at length, as well as any other condition that is affected by IL-23, IL-12 and/or IFNα.

[0136] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating asthma.

[0137] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating an inflammatory bowel disease.

[0138] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating Crohn's disease.

[0139] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating ulcerative colitis.

[0140] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating rheumatoid arthritis.

[0141] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating psoriasis.

[0142] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating allergic rhinitis.

[0143] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating atopic or contact dermatitis.

[0144] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating delayed hypersensitivity reactions.

[0145] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating lupus.

[0146] The present disclosure further relates to the use of one or more of the TYK2 inhibitors disclosed herein for making a medicament for treating multiple sclerosis.

[0147] Compounds of formula (I) have utility in treating conditions associated with the modulation of the function of IL12, IL-23 or IFNα, and particularly the selective inhibition of function of IL-23, IL-12 and/or IFNα, by acting on TYK2 to mediate signal

transduction. Such conditions include IL-23-, IL-12-, or IFNα-associated diseases in which pathogenic mechanisms are mediated by these cytokines.

[0148] In view of their activity as modulators of IL-23-, IL-12 and IFNα-stimulated cellular responses, compounds of Formula (I) are useful in treating IL-23-, IL-12- or IFNα-associated diseases including, but not limited to, inflammatory diseases such as Crohn's disease, ulcerative colitis, asthma, graft versus host disease, allograft rejection, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosis, cutaneous lupus, lupus nephritis, discoid lupus erythematosus, psoriasis; auto-inflammatory diseases including CAPS, TRAPS, FMF, adult onset stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis; metabolic diseases including type 2 diabetes, atherosclerosis, myocardial infarction; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma-related bone disorder; proliferative disorders such as acute myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, oncologic and viral diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS, respectively.

[0149] More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosis, cutaneous lupus, lupus nephritis, discoid lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory

reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, keloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovasculization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia [should this be hypoxia], vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase syndase-2, and pemphigus vulgaris. Preferred methods of treatment are those wherein the condition is selected from Crohn's disease, ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris. Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusions injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction. Another preferred method of treatment is one in which the condition is multiple myeloma.

[0150] The methods of treating IL-23-, IL-12 and/or IFNα-associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions.

[0151] Examples of such other therapeutic agents include, but are not limited to, corticosteroids, rolipram, calphostin, cytokine-suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, PROGRAF®); anti-malarials such as hydroxychloroquine; cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or RAPAMUNE®) or derivatives thereof.

[0152] The above other therapeutic agents, when employed in combination with the compounds described herein, may be used, for example, in those amounts indicated in the *Physicians' Desk Reference* (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

[0153] The compounds and compositions described herein may be administered via a variety of routes.

[0154] Orally administered preparations can be in the form of solids, liquids, emulsions, suspensions, or gels, or in dosage unit form, for example as tablets or capsules. Tablets can be compounded in combination with other ingredients customarily used, such as tale, vegetable oils, polyols, gums, gelatin, starch, and other carriers. The TYK2 inhibitors can be dispersed in or combined with a suitable liquid carrier in solutions, suspensions, or emulsions.

[0155] Parenteral compositions intended for injection, either subcutaneously, intramuscularly, or intravenously, can be prepared as liquids or solid forms for solution in liquid prior to injection, or as emulsions. Such preparations are sterile, and liquids to be injected intravenously should be isotonic. Suitable excipients are, for example, water, dextrose, saline, and glycerol.

[0156] Administration of pharmaceutically acceptable salts of the substances described herein is included within the scope of the present disclosure. Such salts can be prepared from pharmaceutically acceptable non-toxic bases including organic bases and inorganic bases. Salts derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, basic amino acids, and the like. For a helpful discussion of pharmaceutical salts, see S. M. Berge et al., *Journal of Pharmaceutical Sciences* 66:1-19 (1977) the disclosure of which is hereby incorporated by reference.

[0157] Substances for injection can be prepared in unit dosage form in ampules, or in multidose containers. The TYK2 inhibitors or compositions comprising one or more TYK2 inhibitors to be delivered, can be present in such forms as suspensions, solutions, or emulsions in oily or preferably aqueous vehicles. Alternatively, a salt of theTYK2 inhibitor can be in lyophilized form for reconstitution, at the time of delivery, with a suitable vehicle, such as sterile pyrogen-free water. Both liquids as well as lyophilized forms that are to be reconstituted will comprise agents, preferably buffers, in amounts necessary to suitably adjust the pH of the injected solution. For any parenteral use, particularly if the formulation is to be administered intravenously, the total concentration of solutes should be controlled to make the preparation isotonic, hypotonic, or weakly hypertonic. Nonionic materials, such as sugars, are preferred for adjusting tonicity, and sucrose is particularly preferred. Any of these forms can further comprise suitable formulary agents, such as starch or sugar, glycerol or saline. The compositions per unit dosage, whether liquid or solid, can contain from 0.1% to 99% of polynucleotide material.

Methods Relating to Inhibition of TYK2 & Modulation of IL-12, IL-23 and/or IFNα

[0158] Described herein are compounds of Formula (I), or pharmaceutically acceptable isomers, racemates, hydrates, solvates, or salts thereof, useful for the modulation of IL-12, IL-23 and/or IFNα by acting on TYK2 to cause signal transduction inhibition.

[0159] Also described herein are methods of treating diseases associated with the modulation of IL-12, IL-23, and/or IFNα, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to Formula (I).

[0160] Also described herein are methods for treating proliferative, metabolic, allergic, autoimmune and inflammatory diseases (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention.

[0161] Also described herein are methods of treating an inflammatory or autoimmune disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases) comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I).

[0162] Also described herein are methods for treating a disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I), wherein the disease is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), lupus nephritis, cutaneous lupus, inflammatory bowel disease, psoriasis, Crohn's Disease, psoriatic arthritis, Sjögren's syndrome, systemic scleroderma, ulcerative colitis, Graves' disease, discoid lupus erythematosus, adult onset Stills, systemic onset juvenile idiopathic arthritis, gout, gouty arthritis, type 1 diabetes, insulin dependent diabetes mellitus, sepsis, septic shock, Shigellosis, pancreatitis (acute or chronic), glomerulonephritis, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, myasthenia gravis, pancreatitis (acute or chronic), ankylosing spondylitis, pemphigus vulgaris, Goodpasture's disease, antiphospholipid syndrome, idiopathic thrombocytopenia, ANCA-associated vasculitis, pemphigus, Kawasaki disease, Chronic Inflammatory

Demyelinating Polyneuropathy (CIDP), dermatomyositis, polymyositis, uveitis, Guillain-Barre syndrome, autoimmune pulmonary inflammation, autoimmune thyroiditis, autoimmune inflammatory eye disease, and chronic demyelinating polyneuropathy.

[0163] Also described herein are methods of treating an inflammatory or autoimmune disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of said diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I), wherein the disease is selected from systemic lupus erythematosus (SLE), lupus nephritis, cutaneous lupus, Crohn's Disease, ulcerative colitis, type 1 diabetes, psoriasis, rheumatoid arthritis, systemic onset juvenile idiopathic arthritis, ankylosing spondylitis, and multiple sclerosis.

[0164] Also described herein are methods for treating rheumatoid arthritis (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of rheumatoid arthritis), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I).

[0165] Also described herein are methods of treating a condition (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these conditions) comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I), wherein the condition is selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, solid tumors, ocular neovasculization, and infantile haemangiomas, B cell lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, inflammatory bowel disease, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evans syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjögren's syndrome, peripheral neuropathies, pemphigus vulgaris and asthma.

[0166] Also described herein are methods of treating an IL-12, IL-23, and/or IFNα mediated disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I).

[0167] Also described herein are methods of treating an IL-12, IL-23 and/or IFNα mediated disease (or use of the compounds of the present invention for the manufacture of a medicament for the treatment of these diseases), comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Formula (I), wherein the IL-12, IL-23 and/or IFNα mediated disease is a disease modulated by IL-12, IL-23 and/or IFNα.

[0168] Also described herein are methods of treating diseases, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of Formula (I) in combination with other therapeutic agents.

[0169] Also described herein are compounds of Formula (I) for use in therapy. In some embodiments, the compounds of Formula (I) are selected from exemplified compounds or combinations of exemplified compounds or other embodiments herein. In some embodiments, the compounds of Formula (I) are selected from those presented in table 1.

[0170] In other embodiments the compounds of Formula (I) have an IC_{50}<1000nM in at least one of the assays described herein.

Methods Relating to the Treatment of Cancer

[0171] As used herein cancer is defined herein as "an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize." As such, both metastatic and non-metastatic cancers can be treated by the disclosed methods.

[0172] Described herein are methods for treating cancer in a human or mammal, comprising administering, to a human or mammal with cancer, an effective amount of

one or more compounds of Formula (I) or pharmaceutically acceptable isomers, racemates, hydrates, solvates, or salts thereof.

[0173] Also described herein are methods for treating a human or mammal diagnosed with cancer, comprising administering, to a human or mammal with cancer, an effective amount of one or more compounds of Formula (I) or pharmaceutically acceptable isomers, racemates, hydrates, solvates, or salts thereof.

[0174] Also described herein are methods for treating cancer in a human or mammal, comprising co-administering, to a human or mammal with cancer, an effective amount of one or more compounds of Formula (I) or pharmaceutically acceptable isomers, racemates, hydrates, solvates or salts thereof, in combination with an effective amount of one or more chemotherapeutic agent or chemotherapeutic compound.

[0175] Also described herein are methods for treating a human or mammal diagnosed with cancer, comprising administering, to a human or mammal with cancer, an effective amount of one or more compounds of Formula (I) or pharmaceutically acceptable isomers, racemates, hydrates, solvates or salts thereof, in combination with an effective amount of one or more chemotherapeutic agent or chemotherapeutic compound.

[0176] The following are non-limiting examples of malignant and non-malignant cancers. Acute Lymphoblastic; Acute Myeloid Leukemia; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; Appendix Cancer; Basal Cell Carcinoma; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bone Cancer; Osteosarcoma and Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Childhood; Central Nervous System Embryonal Tumors; Cerebellar Astrocytoma; Cerebral Astrocytoma/Malignant Glioma; Craniopharyngioma; Ependymoblastoma; Ependymoma; Medulloblastoma; Medulloepithelioma; Pineal Parenchymal Tumors of Intermediate Differentiation; Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma; Visual Pathway and Hypothalamic Glioma; Brain and Spinal Cord Tumors; Breast Cancer; Bronchial Tumors; Burkitt Lymphoma; Carcinoid Tumor; Carcinoid Tumor, Gastrointestinal;

Central Nervous System Atypical Teratoid/Rhabdoid Tumor; Central Nervous System Embryonal Tumors; Central Nervous System Lymphoma; Cerebellar Astrocytoma; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Chordoma, Childhood; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Colon Cancer; Colorectal Cancer; Craniopharyngioma; Cutaneous T-Cell Lymphoma; Esophageal Cancer; Ewing Family of Tumors; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastrointestinal Carcinoid Tumor; Gastrointestinal Stromal Tumor (GIST); Germ Cell Tumor, Extracranial; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma; Glioma, Childhood Brain Stem; Glioma, Childhood Cerebral Astrocytoma; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer; Histiocytosis, Langerhans Cell; Hodgkin Lymphoma; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma; Intraocular Melanoma; Islet Cell Tumors; Kidney (Renal Cell) Cancer; Langerhans Cell Histiocytosis; Laryngeal Cancer; Leukemia, Acute Lymphoblastic; Leukemia, Acute Myeloid; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer; Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoma, AIDS-Related; Lymphoma, Burkitt; Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin; Lymphoma, Non-Hodgkin; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom; Malignant Fibrous Histiocytoma of Bone and Osteosarcoma; Medulloblastoma; Melanoma; Melanoma, Intraocular (Eye); Merkel Cell Carcinoma; Mesothelioma; Metastatic Squamous Neck Cancer with Occult Primary; Mouth Cancer; Multiple Endocrine Neoplasia Syndrome, (Childhood); Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelodysplastic/Myelo-proliferative Diseases; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Adult Acute; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Neuroblastoma; Non-Small Cell Lung Cancer;

Oral Cancer; Oral Cavity Cancer; Oropharyngeal Cancer; Osteosarcoma and Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Islet Cell Tumors; Papillomatosis; Parathyroid Cancer; Penile Cancer; Pharyngeal Cancer; Pheochromocytoma; Pineal Parenchymal Tumors of Intermediate Differentiation; Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Primary Central Nervous System Lymphoma; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Pelvis and Ureter, Transitional Cell Cancer; Respiratory Tract Carcinoma Involving the NUT Gene on Chromosome 15; Retinoblastoma; Rhabdomyosarcoma; Salivary Gland Cancer; Sarcoma, Ewing Family of Tumors; Sarcoma, Kaposi; Sarcoma, Soft Tissue; Sarcoma, Uterine; Sézary Syndrome; Skin Cancer (Nonmelanoma); Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma; Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Supratentorial Primitive Neuroectodermal Tumors; T-Cell Lymphoma, Cutaneous; Testicular Cancer; Throat Cancer; Thymoma and Thymic Carcinoma; Thyroid Cancer; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Urethral Cancer; Uterine Cancer, Endometrial; Uterine Sarcoma; Vaginal Cancer; Vulvar Cancer; Waldenström Macroglobulinemia; and Wilms Tumor.

[0177] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined

with any and all other elements from any embodiment to describe an additional embodiment.

Methods for Making the Compounds of Formula (I)

[0178] Compounds having the structure of Formula (I), may be synthesized using standard synthetic techniques known to those of skill in the art. To this end, the reactions, processes and synthetic methods described herein are not limited to the specific conditions described in the following experimental section, but rather are intended as a guide to one with suitable skill in this field. For example, reactions may be carried out in any suitable solvent, or other reagents to perform the transformation[s] necessary. Generally, suitable solvents are protic or aprotic solvents which are substantially non-reactive with the reactants, the intermediates or products at the temperatures at which the reactions are carried out (i.e., temperatures which may range from the freezing to boiling temperatures). A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction, suitable solvents for a particular work-up following the reaction may be employed.

[0179] Unless otherwise indicated, conventional methods of mass spectroscopy (MS), liquid chromatography-mass spectroscopy (LCMS), NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques, and pharmacology are employed. Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 7th Edition, John Wiley and Sons, Inc (2013). Alternate reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions. As necessary, the use of appropriate protecting groups may be required. The incorporation and cleavage of such groups may be carried out using standard methods described in Peter G. M. Wuts and Theodora W. Green, Protecting Groups in Organic Synthesis, 4th Edition, Wiley-Interscience. (2006). All starting materials and reagents are commercially available or readily prepared.

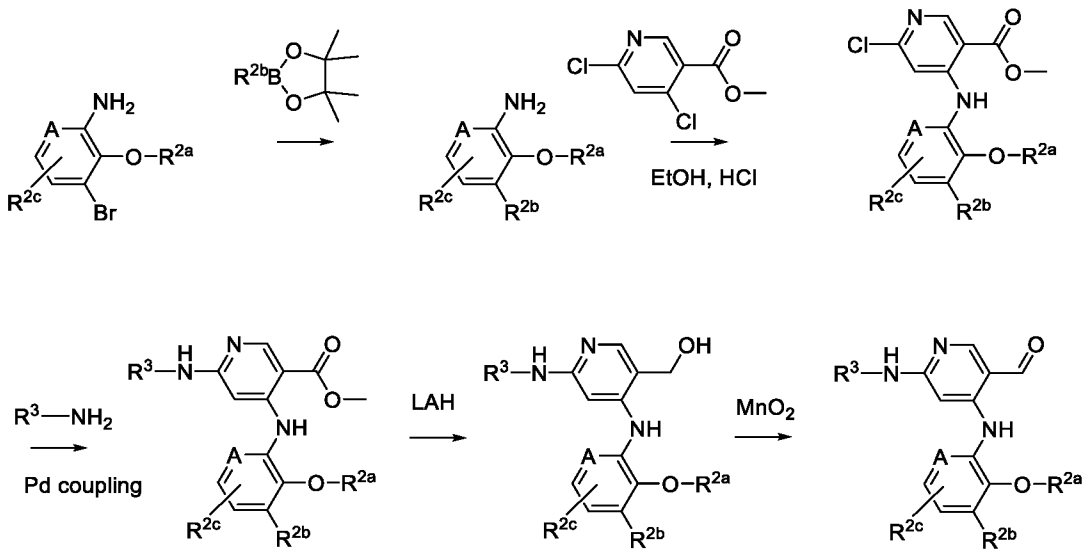
[0180] Compounds of Formula (I) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1, 2 and 3. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

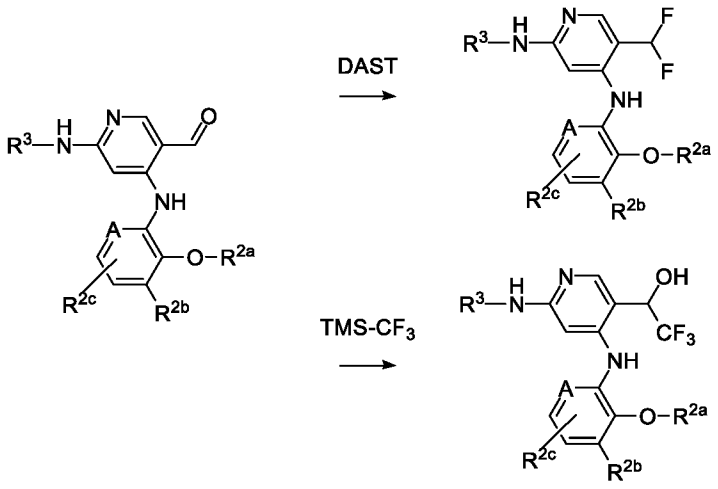
Compounds of formula (I) are prepared according to the general schemes presented below.

R^1 is difluoromethyl or 2,2,2-trifluoroethan-1-ol

[0181] 3-bromo-2-R^{2a} oxyaniline (A = CH) or 4-bromo-3-R^{2a} oxypyridin-2-amine (A = N), optionally substituted with R^{2c}, is coupled with a boronate reagent containing R^{2b}. The resulting aniline or aminopyridine is heated with methyl 4,6-dichloronicotinate, and then coupled with R^3—NH_2.The methyl ester is reduced to the corresponding alcohol, using a suitable reducing agent (e.g. LiAlH4), and then oxidized to the aldehyde using a suitable oxidizing agent (e.g. MnO_2). The aldehyde is treated with diethylamino sulfur trifluoride (DAST) to provide R^1 as a difluoromethyl group. Alternatively, the aldehyde is treated with TMS-CF_3 to provide R^1 as the 2,2,2-trifluoroethan-1-ol derivative.

Scheme 1: Compounds of formula (I), wherein R^1 is difluoromethyl or 2,2,2-trifluoroethan-1-ol

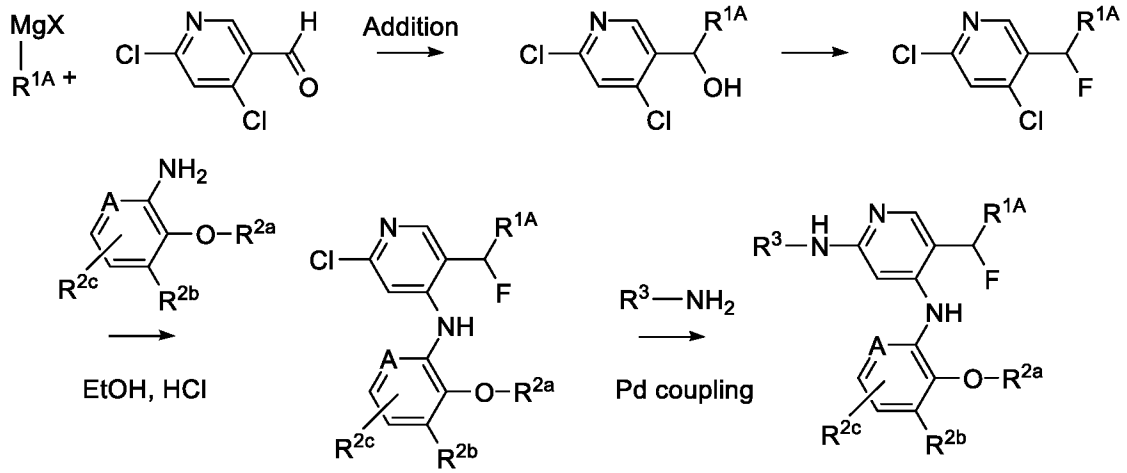




R1 is CHFR1A

[0182] 4,6-dichloronicotinaldehyde is reacted with R1A-magnesium halide (e.g. bromide) via an addition reaction, to provide (4,6-dichloropyridin-3-yl)-R1A-methanol. The hydroxyl group is converted to the corresponding benzylic fluoride by treatment with DAST. The R2- aniline or aminopyridine is reacted the 2,4-dichloropyridine to afford the 4-anilino adduct which is then coupled to the R3 amine to provide final compounds of formula (I).

Scheme 2: Compounds of formula (I), wherein R1 is CHFR1A



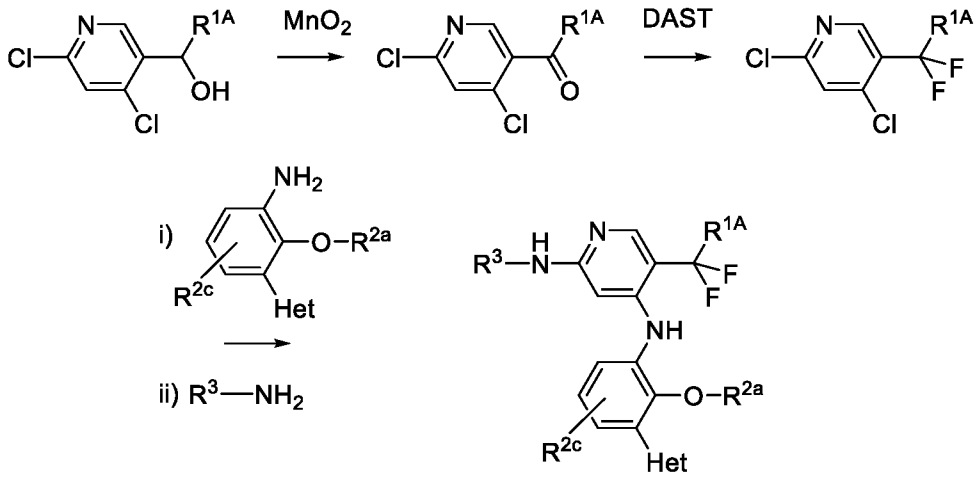
R1 is CF2R1A

[0183] (4,6-Dichloropyridin-3-yl)-R1A-methanol is oxidized to the corresponding ketone using a suitable oxidizing agent (e.g. , manganese dioxide), then treated with a fluorinating agent such as DAST to provide the CF2R1A. The R2- aniline or aminopyridine is reacted the 2,4-

dichloropyridine to afford the 4-anilino adduct which is then coupled to the R^3 amine to provide final compounds of formula (I).

[0184]

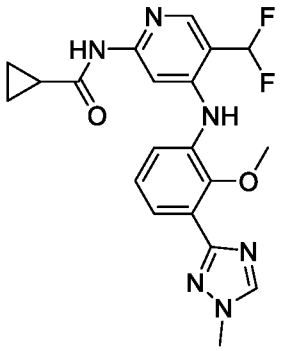
Scheme 3: Compounds of formula (I), wherein R^1 is CF_2R^{1A}



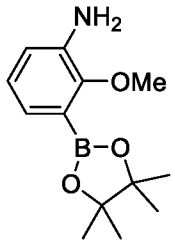
EXAMPLES

EXAMPLE 1

[0185] N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (Compound 1)

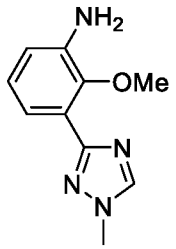


STEP 1: 2-Methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



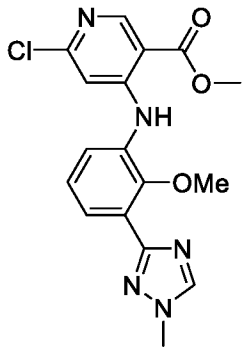
To a solution of 3-bromo-2-methoxy-aniline (2.0 g, 9.9 mmol) in 1,4-dioxane (100 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.0 g, 11.9 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (724 mg, 0.99 mmol) and potassium acetate (1.9 g, 19.8 mmol) under a nitrogen atmosphere. The resultant mixture was heated at reflux at 100°C for 4 hours. The mixture was cooled, filtered and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column eluting with ethyl acetate/petroleum ether (3:1). Desired fractions were combined and concentrated to yield 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.0 g, 80%).

STEP 2: 2-Methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)aniline



To a solution of 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.0 g, 8.0 mmol) in 1,4-dioxane (80 mL) and water (20 mL) was added 3-bromo-1-methyl-1*H*-1,2,4-triazole (1.5 g, 9.6 mmol), 2-dicyclohexylhosphino-2',4',6'-triisopropylbiphenyl (760 mg, 1.6 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (67 mg, 0.8 mmol) and potassium phosphate tribasic (3.4 g, 16 mmol) under a nitrogen atmosphere. The mixture was stirred at 90°C for 4 hours. The reaction mixture was cooled, filtered and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column eluting with 5% methanol in dichloromethane. Desired fractions were combined and concentrated to yield 2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)aniline (1.4 g, 88%).

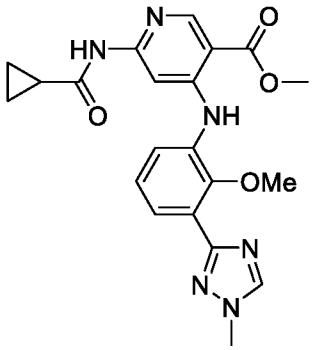
STEP 3: Methyl 6-chloro-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino) nicotinate



To a solution of 2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)aniline (300 mg, 1.47 mmol, 1eq) and methyl 4,6-dichloronicotinate (303 mg, 1.47 mmol. 1 eq) in ethanol (9.9 mL) was added concentrated hydrochloric acid (100 uL) and stirred overnight at 85°C. The solvent was removed in vacuo, and the resulting residue purified on a silica gel column eluting with dichloromethane/methanol (10:1) to yield methyl 6-chloro-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)nicotinate (200 mg, 36%).

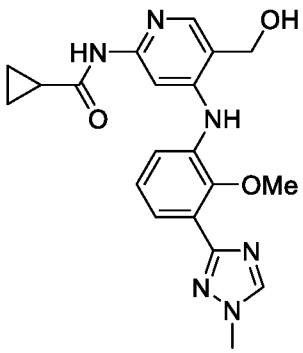
STEP 4: Methyl 6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-

yl)phenyl)amino)nicotinate



Into a vial was placed cyclopropanecarboxamide (170 mg, 2.00 mmol), methyl 6-chloro-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)nicotinate (498 mg, 1.33 mmol), BrettPhos Pd G3 (121 mg, 0.13 mmol), BrettPhos (71 mg, 0.13 mmol), cesium carbonate (868 mg, 2.66 mmol) and 1,4-dioxane (20 mL). The resulting solution was stirred under nitrogen at 90°C for 2 hours. The solvent was evaporated under reduced pressure, and the resulting residue purified on a silica gel column, eluting with ethyl acetate/petroleum ether (2:1). The product was further purified by Prep-HPLC to yield methyl 6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)nicotinate (27.9 mg, 15%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 8.77 (s, 1H), 8.51 (s, 1H), 8.12 (s, 1H), 7.70-7.60 (m, 2H), 7.32 (m, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 3.74 (s, 3H), 1.88 (m, 1H), 0.96 (m, 2H), 0.88 (m, 2H). (ES, *m/z*): $[M+H]^+$ 423.15.

STEP 5: *N*-(5-(Hydroxymethyl)-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide



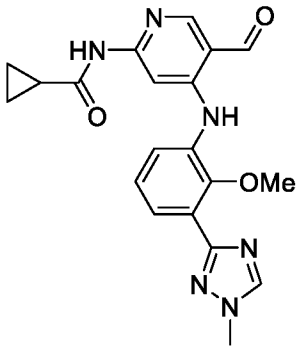
To a solution of methyl 6-(cyclopropanecarboxamido)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)nicotinate (50 mg, 0.12 mmol) in tetrahydrofuran (2 mL) at 0°C was added lithium aluminum hydride (23 mg, 0.6 mmol). The mixture was allowed to warm to ambient temperature and stirred there for 2 hours. The reaction mixture was quenched with

water, and then the resulting suspension was extracted with of ethyl acetate (3 x 50 mL) and the organic layers were combined and dried over anhydrous sodium sulfate. The crude product was purified by Prep-HPLC to afford *N*-(5-(hydroxymethyl)-4-((2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (3.1 mg, 7%) as a solid.

H^1-NMR (CD_3OD, 400 MHz) δ 8.54 (s, 1H), 7.95 (s, 1H), 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.53 (dd, J = 7.9, 1.7 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 6.44 (d, J = 3.8 Hz, 1H), 4.78 (d, J = 0.9 Hz, 2H), 4.54 (qd, J = 7.0, 1.2 Hz, 1H), 4.05 (s, 3H), 3.68 (s, 3H), 1.76 (tt, J = 7.4, 4.5 Hz, 1H), 1.09 (dt, J = 4.7, 3.2 Hz, 2H), 1.02 (dt, J = 7.9, 3.2 Hz, 2H).

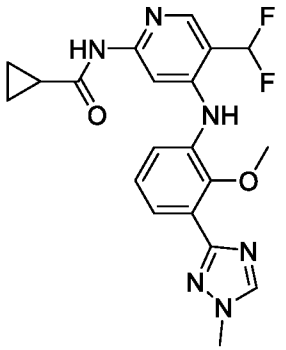
(ES, *m/z*): $[M+H]^+$= 395.15.

STEP 6: N-(5-formyl-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide



In a round-bottom flask purged and maintained was placed N-(5-(hydroxymethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (500 mg, 1.3 mmol), chloroform (10 mL), and manganese(IV) oxide (3.3 g, 38 mmol). The resulting mixture was stirred overnight at 60 °C. The solids were filtered out and the filtrated concentrated. The mixture was purified by column chromatography eluting with 0-10% methanol in dichloromethane. Desired fractions were combined and concentrated to yield N-(5-formyl-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (300 mg, 60%).

STEP 7: N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (Compound 1)

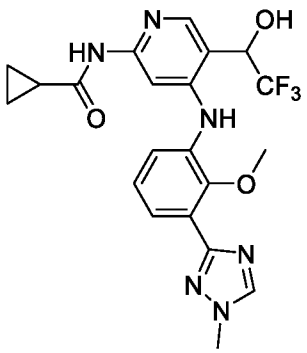


To a solution of N-(5-formyl-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (300 mg, 0.76 mmol) in 1,2-dichloroethane (10 mL) under nitrogen at ambient temperature was added bis(2-methoxyethyl)aminosulfur trifluoride (510 mg, 2.3 mmol). The resulting solution was stirred overnight at 70 ℃, concentrated under vacuum, then purified by Prep-HPLC. Desired fractions were combined to yield N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (12.9 mg, 4%) as a solid.

H^1-NMR (CD_3OD, 400 MHz) δ 8.51 (s, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.70 -7.65 (m, 1H), 7.58-7.54 (m, 1H), 7.35-7.25 (m, 1H), 7.15-6.85 (m, 1H), 4.05 (s, 3H), 3.69 (s, 3H), 1.90-1.80 (m, 1H), 1.10-0.95 (m, 4H).

[0186] EXAMPLE 2

N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclopropanecarboxamide (Compound 2)



To a stirred solution of N-(5-formyl-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide (50 mg, 0.13 mmol) in THF (2 mL) were added (trimethylsilyl)trifluoromethane (50 mg, 0.13 mmol), potassium carbonate (35 mg,

0.255 mmol) and 1M tetrabutylammonium fluoride in THF (0.5 mL) dropwise at 0°C. The resulting mixture was stirred overnight at room temperature. The solvent was removed under vacuum. The crude product was purified by Prep-HPLC to yield N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclopropanecarboxamide (5.4 mg, 7% yield) as the trifluoroacetate salt.

^{1}H NMR (CD_3OD, 400 MHz,) δ 8.55 (s, 1H), 8.14 (s, 1H), 7.90 (dd, J = 7.8, 1.8 Hz, 1H), 7.49 (dd, J = 7.9, 1.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 6.37 (s, 1H), 5.61 (q, J = 6.6 Hz, 1H), 4.05 (s, 3H), 3.66 (s, 3H), 1.74 (m, 1H), 1.15-1.09 (m, 2H), 1.06-1.00 (m, 2H).

TYK2 ACTIVITY OF COMPOUNDS OF FORMULA I

[0187] EXAMPLE 3

TYK2 JH2 NanoBRET™ assay

HEK293T cells were transfected with NanoLuc-TYK2 JH2 Fusion Vector (Promega, customized) using Trans-IT reagent (Mirus, #MIR2700) and incubated for overnight in 37^{0}C incubator. Cells were harvested using trypLE and resuspended into phenol-free opti-MEM (Life technologies, #11058-021) at 0.25X10^6/ml. Add 85µL of cell suspension into white, polypropylene, 96-well plates (Corning, #3600). 90µL of cells were used for no tracer control samples. 5µL of diluted NanoBRET K10 tracer (Promega, #CS1810C122) were added to cells to a final concentration of 0.5µM. Test compounds were diluted into DMSO, and then phenol-free opti-MEM to 10X of final concentration. 10µL of diluted compounds were added into each well. The cells were incubated with test compound and tracer for 2 hours. 3XNanoBRET™ Nano-Glo® Substrate and Extracellular NanoLuc® Inhibitor mixture was prepared and 50 µL of the mixture were added into the wells and mixed. BRET signal was measured using Tecan SPARK plate reader with donor and acceptor emissions at 450nM and 610nM, respectively. NanoBRET signal was determined by using the ratio of acceptor signal and donor signal. Binding on TYK2 JH2 domain was calculated by remaining NanoBRET signal relative to DMSO controls and plotted using PRISM (GraphPad) to determine a 50% inhibitory concentration (IC_{50}).

IC_{50} values are provided for the compounds of the present invention in Table 2, below.

With respect to TYK2 activity:

"A" denotes an IC_{50} of less than 5nM;

"B" denotes an IC_{50} of from 5nM to less than 50nM;

"C" denotes an IC_{50} of from 50nM to less than 500nM; and

"D" denotes an IC_{50} of 500nM or more.

Table 2

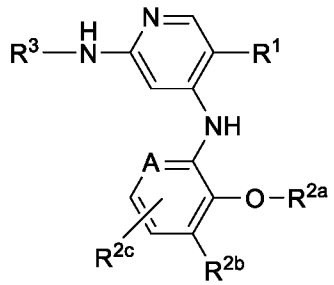
Example	IC_{50}
1	B
2	A

[0188] This application claims the benefit of priority to U.S. Provisional Application No. 63/028,447, filed May 21, 2020, which application is hereby incorporated by reference in its entirety.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the structure of formula (I):

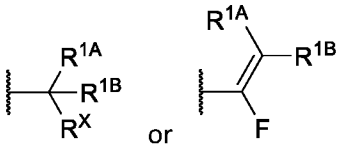


(I)

or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, or salt thereof, wherein:

A is N or CR^{2c};

R^1 is



wherein

R^X is F, O-R^{1C} or N(R^{1C})R^{1D};

R^{1A} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1B} is H, halogen, -C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$

R^{1C} is H,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$;

R^{1D} is H, halogen,-C_{1-4} alkyl, -C_{1-4} haloalkyl, cycloalkyl, heterocycloalkyl, halocycloalkyl, heteroaryl, -$(CH_2)_nCN$, -$(CH_2)_nNRR$, -$(CH_2)_nOR$, -$(CH_2)_nC(=O)R$, -$(CH_2)_nC(=O)OR$, -$(CH_2)_nC(=O)NRR$; or

R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring, optionally containing an O, N or S atom;

and wherein R^1 comprises at least one Fluorine atom;

R^{2a} is H, C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^{2b} is H, −CN, −C(O)OH, −C(O)OC_{1-4}alkyl, −C(O)NR^5R^6, or 5- or 6-membered heteroaryl, wherein R^{2b} is substituted with 0-2 R';

R^{2c} is H, halo, −CN, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4}haloalkyl;

R^3 is H, C_{2-4} alkoxy, −C(O)R^7, carbocycle, heterocycle, aryl or heteroaryl, wherein R^3 is substituted with 0-2 R';

R^5 is H or C_{1-4} alkyl;

R^6 is H, C_{1-4} alkyl, −$(CH_2)_m$−carbocycle, −$(CH_2)_m$−heterocycle, −$(CH_2)_m$−aryl or −$(CH_2)_m$−heteroaryl;

R^7 is C_{1-4} alkyl, −$(CH_2)_n$−OH, −$(CH_2)_n$−OC_{1-4}alkyl, −$(CH_2)_n$−NH_2, −$(CH_2)_n$−NHC_{1-4}alkyl,

−$(CH_2)_n$−N(C_{1-4}alkyl)(C_{1-4}alkyl), −$(CH_2)_n$−carbocycle, −$(CH_2)_n$−heterocycle , −$(CH_2)_m$−aryl, −$(CH_2)_m$−heteroaryl or halocycloalkyl, wherein R^7 is substituted with 0-2 R';

R' is −CN, −NO_2, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, alkoxyalkyl, carbocycle, −$(CH_2)_q$−NRR, −$(CH_2)_q$−C(O)R, −$(CH_2)_q$−C(O)OR, −$(CH_2)_q$−C(O)NRR, −$(CH_2)_q$−NHC(O)R, −$(CH_2)_q$−$S(O)_2$R, -$(CH_2)_q$-carbocycle or -$(CH_2)_q$-heterocycle;

each R is, independently, H, C_{1-4} alkyl, carbocycle or heterocycle;

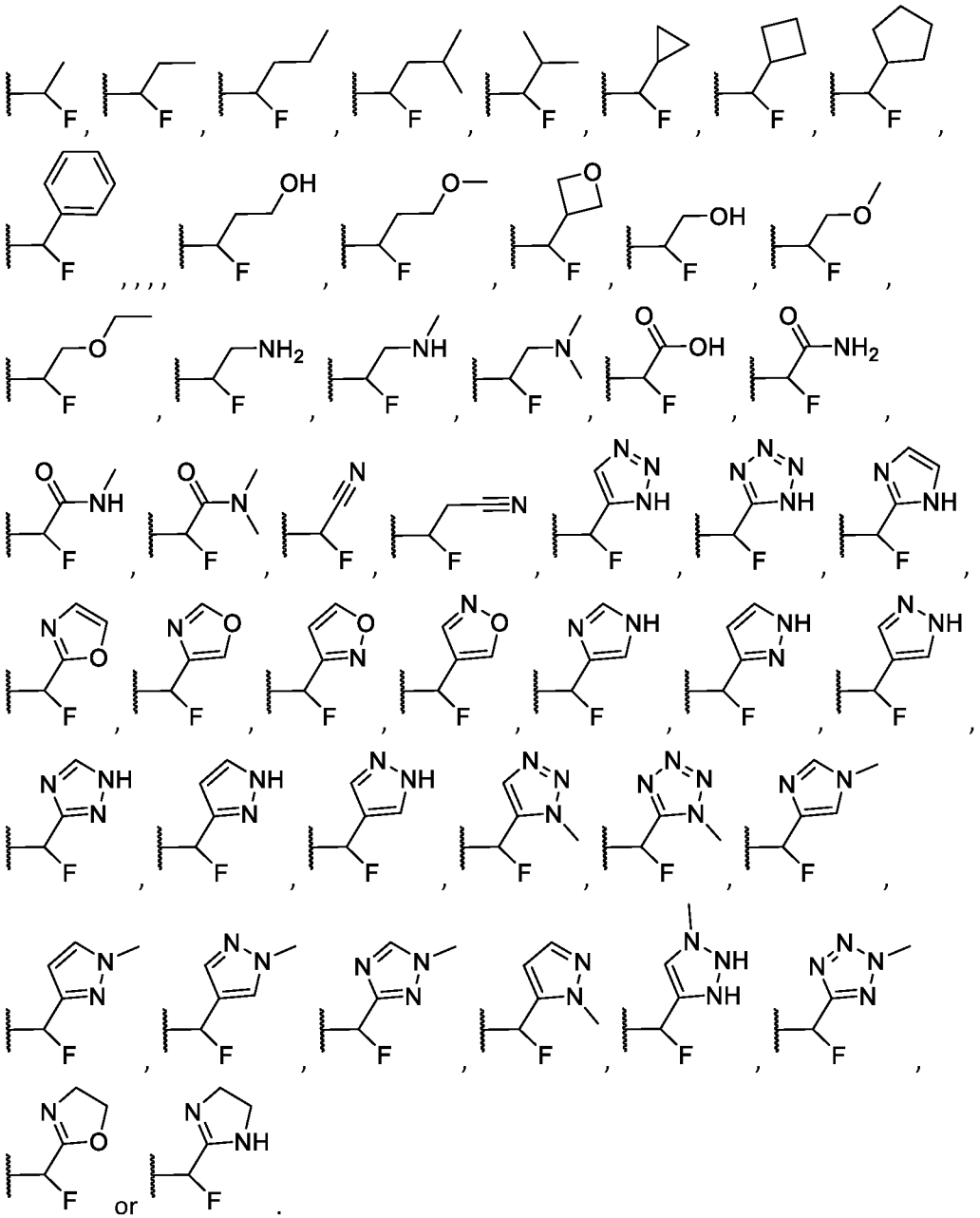
m is 0-2;

n is 0-2; and

q is 0-4.

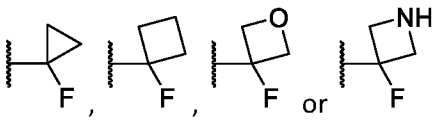
2. A compound of claim **1**, wherein R^X is F.

3. A compound of claim **1**, wherein R^1 is



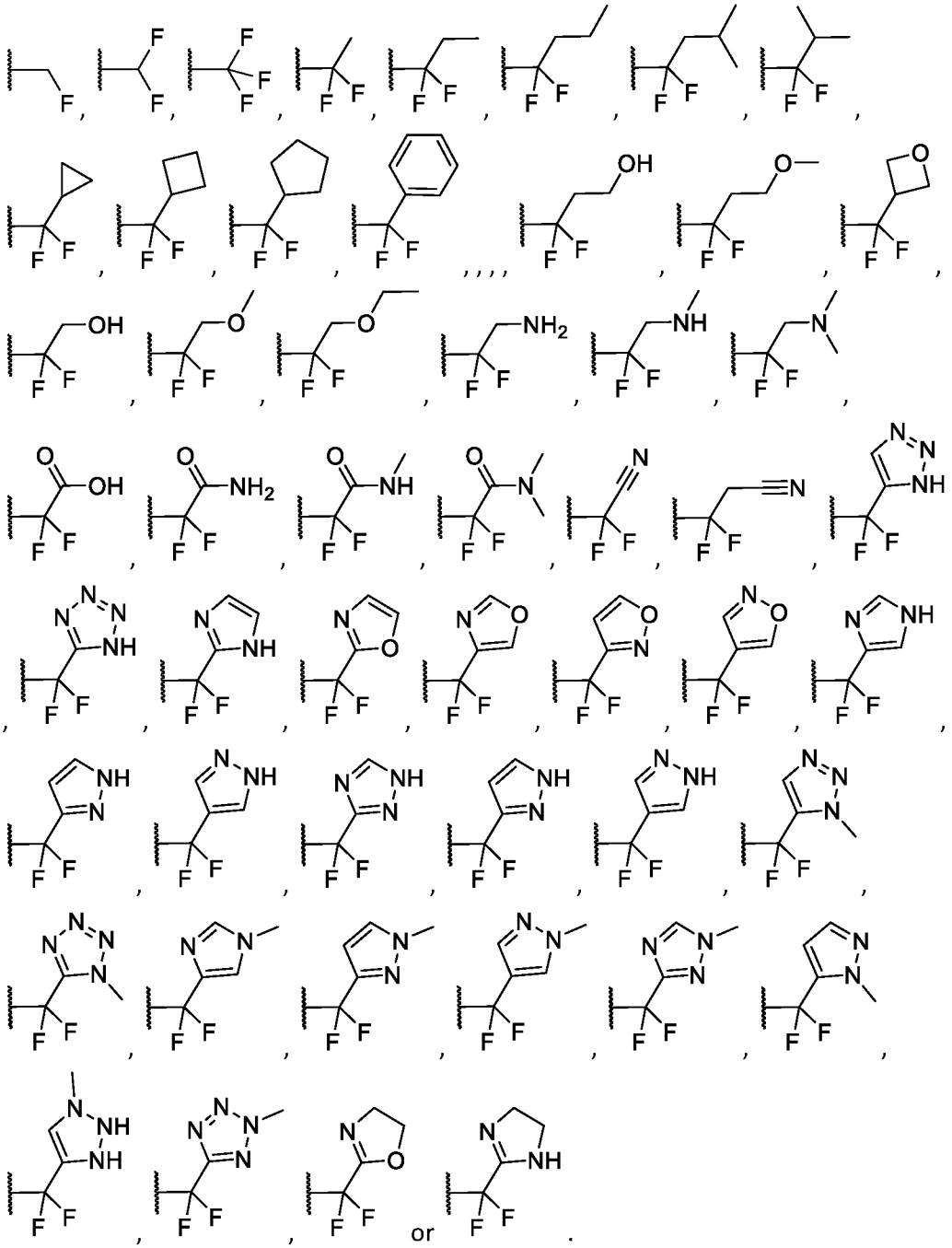
4. A compound of claim **1**, wherein R^X is F and R^{1A} and R^{1B}, together with the C atom to which they are attached, form a 3- or 4- membered ring.

5. A compound of claim **1**, wherein R^1 is



6. A compound of claim **1**, wherein R^X is F and R^{1A} is F.

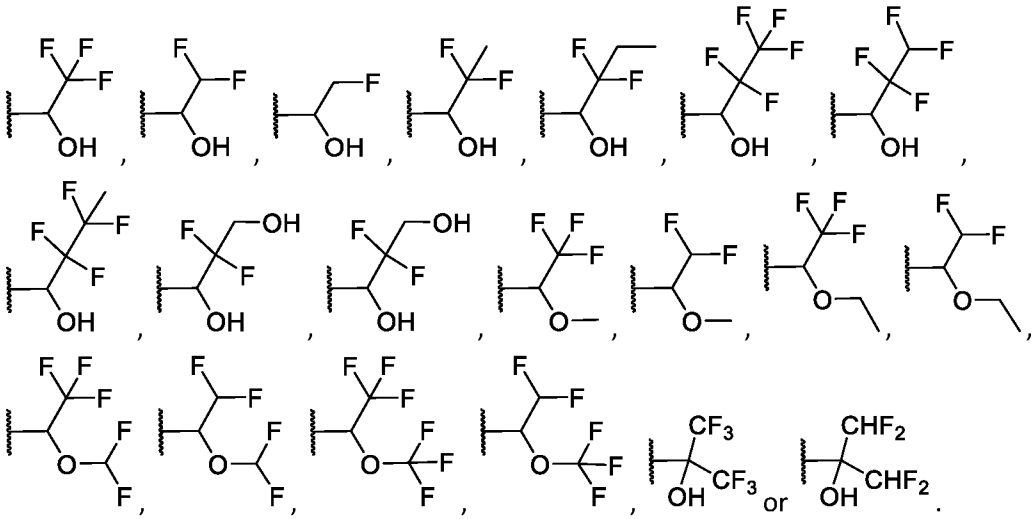
7. A compound of claim **1**, wherein R^1 is



8. A compound of claim **1**, wherein R^X is O-R^{1C}.

9. A compound of claim **1**, wherein R^X is OH or OMe.

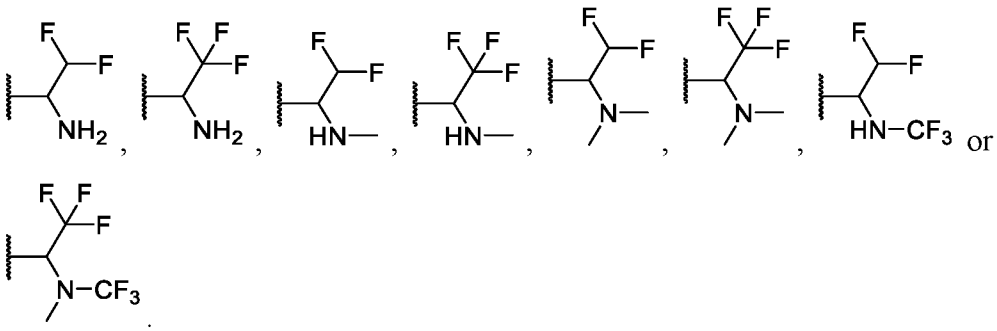
10. A compound of claim **1**, wherein R^1 is



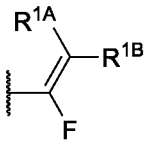
11. A compound of claim **1**, wherein R^X is $N(R^{1C})R^{1D}$.

12. A compound of claim **1**, wherein R^X is NH_2, NHMe or NMe_2.

13. A compound of claim **1**, wherein R^1 is

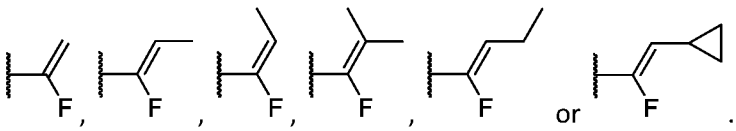


14. A compound of claim **1**, wherein R^1 is



15. A compound of claim **14**, wherein R^{1A} is H and R^{1B} is,-$C_{1\text{-}4}$ alkyl or cycloalkyl.

16. A compound of claim **1**, wherein R^1 is



17. A compound of claim **1**, wherein A is N.

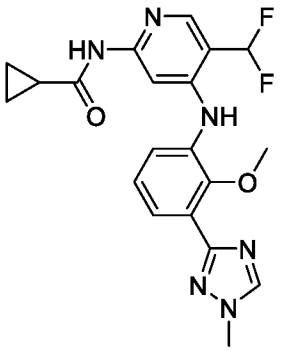
18. A compound of claim **1**, wherein A is CH.

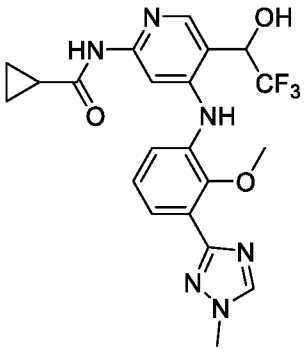
19. A compound of claim **1**, wherein R^{2a} is H, methyl, difluoromethyl, triifluoromethyl ethyl, or fluoroethyl.
20. A compound of claim **1**, wherein R^{2a} is methyl.
21. A compound of claim **1**, wherein R^{2b} is 5- or 6-membered heteroaryl, substituted with 0-2 R'.
22. A compound of claim **1**, wherein R^{2b} is 5- or 6-membered heteroaryl, substituted with methyl.
23. A compound of claim **1**, wherein R^{2b} is -C(O)OH or -C(O)OC_{1-4}alkyl.
24. A compound of claim **1**, wherein R^{2b} is -C(O)NR^5R^6.
25. A compound of claim **1**, wherein R^{2b} is -C(O)NH-CH_2-carbocycle, -C(O)NH-CH_2-heterocycle, -C(O)NH-CH_2-aryl or -C(O)NH-CH_2-heteroaryl.
26. A compound of claim **1**, wherein R^{2b} is -C(O)NH-CH_2-carbocycle, -C(O)NH-CH_2-heterocycle, -C(O)NH-CH_2-aryl or -C(O)NH-CH_2-heteroaryl, substituted with halo or C_{1-6} alkyl.
27. A compound of claim **1**, wherein R^{2b} is -C(O)NH-CH_2-heterocycle or -C(O)NH-CH_2-heteroaryl, substituted with F or methyl.
28. A compound of claim **1**, wherein R^{2c} is H.
29. A compound of claim **1**, wherein R^3 is $-C(O)R^7$.
30. A compound of claim **29**, wherein R^7 is C_{1-4} alkyl or carbocycle.
31. A compound of claim **29**, wherein R^7 is substituted with 1 or 2 R'.
32. A compound of claim **1**, wherein R^3 is aryl or heteroaryl substituted with 1 or 2 R'.
33. A compound of claim **32**, wherein R' is halo, C_{1-6} alkyl or C_{1-6} alkoxy.
34. A compound having a structure listed in Table 1, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope, or salt thereof.
35. A compound of claim **1**, which is

    N-(5-(difluoromethyl)-4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)pyridin-2-yl)cyclopropanecarboxamide

    or

N-(4-((2-methoxy-3-(1-methyl-1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(2,2,2-trifluoro-1-hydroxyethyl)pyridin-2-yl)cyclopropanecarboxamide





36. A pharmaceutical composition comprising a compound of any one of claims **1** - **35**, or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.
37. The composition of claim **36**, further comprising a pharmaceutically acceptable carrier, adjuvant or vehicle.
38. A method of treating a disease responsive to the inhibition of TYK2 kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition of any one of claims **1** - **35**.
39. The method of claim **38**, wherein the disease is an inflammatory disease.
40. The method of claim **38**, wherein the disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.
41. The method of claim **38**, further comprising administering a second therapeutic agent.
42. A kit comprising a pharmaceutical composition of claim **36** and instructions for use.
43. A compound according to any one of claims **1** - **35** for use in treating an inflammatory disease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis,

rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

44. The use of a compound according to any one of claims **1** - **35** in the manufacture of a medicament for the treatment of an inflammatory disease, in particular wherein the inflammatory disease is asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus or multiple sclerosis.

45. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/033710

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P29/00 C07D401/12 A61K31/4439
ADD.

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)
A61P C07D

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)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/115369 A2 (SCRIPPS RESEARCH INST [US]; LIANG CONGXIN [US] ET AL.) 25 September 2008 (2008-09-25) claims 1, 18, 20-22 page 46; compound 121	1,2,6,7, 18,20, 32,36,37
X	WO 2018/071794 A1 (NIMBUS LAKSHMI INC [US]) 19 April 2018 (2018-04-19)	1-20, 23-33, 36-45
A	claims 11, 39-40	21,22, 34,35
X	WO 2015/069310 A1 (SQUIBB BRISTOL MYERS CO [US]) 14 May 2015 (2015-05-14)	1-20, 23-33, 36-45
A	claims 1, 7, 8 example 30	21,22, 34,35

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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
11 August 2021	20/08/2021

Name and mailing address of the ISA/	Authorized officer
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