

AMIDE COMPOUNDS

[0001] In various embodiments, the present disclosure generally relates to novel compounds, compositions comprising the same, methods of preparing and methods of using the same, e.g., for modulating IL-17A/F activities and/or for treating or preventing a disease or disorder described herein.

BACKGROUND

[0002] Interleukin (IL)-17 is a family of pro-inflammatory cytokines consisting of six known members (IL-17 A through F). IL-17 family cytokines are critical in the maintenance of adaptive and innate immunity. Among the IL-17 family, IL-17A and IL-17F are the most investigated members, which can form homo- and heterodimers (IL-17AA, IL-17AF, and IL-17FF). IL-17 A/F can be released by several types of cells, including T helper 17 (Th17) cells, γ/δ T cells, mast cells, neutrophils, etc., with Th17 cells being the major source. Upon release, the IL-17A/F cytokines act through their corresponding IL-17 receptors, which are formed by homo- or heterodimers of IL-17 receptor A and IL-17 receptor C (IL-17RA and IL-17RC). Specifically, activation of the IL-17 receptor triggers the canonical signaling and gene expression via multiple signaling pathways (*e.g.*, Nuclear factor kappa B, Mitogen-activated protein kinases, and CCAAT/enhancer binding protein-B, etc.), and leads to the subsequent production of inflammatory cytokines, including IL-8, IL-6, IL-1 β , TNF- α , etc., as well as numerous chemokines and other effectors. Despite the contribution in the host defense response to bacterial and fungal infection, the elevated IL-17 A/F cytokines are also key players in autoimmune pathogenesis, through exaggerated inflammatory cascades and the subsequent tissue damage in multiple autoimmune disorders, including but not limited to, psoriasis (Ps), psoriatic arthritis (PsA), ankylosing spondylitis (AS), hidradenitis suppurativa (HS), bone erosion, allograft rejection, multiple sclerosis, etc. In addition, IL-17A and Th17 cells have also been implicated in certain cancers, such as multiple myeloma and hepatocellular carcinoma (HCC).

[0003] Targeting IL-17 A and/or F has been clinically shown as effective for treating autoimmune and/or inflammatory diseases and disorders. For example, biotherapeutics of IL-17-targeted antibody therapies have made significant advances and demonstrated clinical benefits in treating autoimmune diseases. Monoclonal antibodies (mAbs) targeting IL-17A

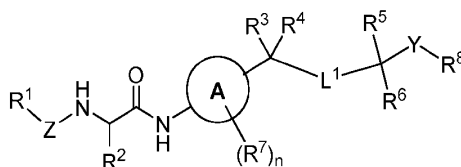
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(*e.g.*, secukinumab and ixekizumab) as well as an antibody against IL-17 receptors (*e.g.*, brodalumab) have been approved by the U.S. Food and Drug Administration for treating patients with autoimmune disorders (*e.g.*, Ps, PsA, and AS). Despite these advancements, small molecule modulators of IL-17 are needed, which can provide an alternative and/or orally available treatments for IL-17-related diseases.

BRIEF SUMMARY

[0004] In various embodiments, the present disclosure is based in part on the discovery that certain novel amide compounds can modulate IL-17A and/or IL-17F and are useful for treating or preventing a disease or disorder associated with IL-17A and/or IL-17F, such as an autoimmune and/or inflammatory disease or disorder described herein.

[0005] In some embodiments, the present disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I,

wherein the variables are defined herein. In some embodiments, the compound of Formula I can have a structure according to a sub-formula selected from Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2, as defined herein. In some embodiments, the present disclosure also provides a compound selected from Table 1 herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure also provides a compound selected from Examples 1-174 herein, or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments of the present disclosure are directed to a pharmaceutical composition comprising one or more compounds of the present disclosure (*e.g.*, a compound of Formula I (*e.g.*, Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), and optionally a pharmaceutically acceptable excipient. The

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pharmaceutical composition described herein can be formulated for different routes of administration, such as for oral administration or parenteral injection.

[0007] Certain embodiments of the present disclosure are directed to a method of treating a disease or disorder associated with IL-17A and/or IL-17F, such as an inflammatory disease or disorder and/or an autoimmune disease or disorder herein, for example, psoriasis, psoriatic arthritis, or ankylosing spondylitis. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition herein.

[0008] In some embodiments, the present disclosure provides a method of treating an inflammatory disease or condition in a subject in need thereof. In some embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition herein. In some embodiments, the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

[0009] The administering in the methods herein is not limited to any particular route of administration. For example, in some embodiments, the administering can be orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, or parenterally. In some embodiments, the administering is orally. In some embodiments, the administering is a parenteral injection, such as an intravenous injection.

[0010] Compounds of the present disclosure can be used as a monotherapy or in a combination therapy. In some embodiments according to the methods described herein, one

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or more compounds of the present disclosure can be administered as the only active ingredient(s).

[0011] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention herein.

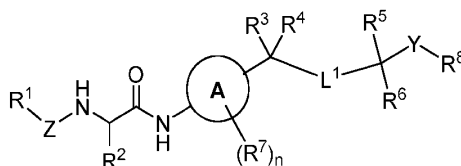
DETAILED DESCRIPTION

[0012] In various embodiments, provided herein are novel compounds, pharmaceutical compositions, methods of preparation and methods of use. The compounds of the present disclosure are generally IL-17A/F modulators, which are also useful for treating various diseases or disorders, such as those described herein, e.g., an autoimmune and/or inflammatory disease or disorder herein, such as psoriasis. As shown in the Examples section, representative compounds herein show potent inhibition in both the IL17AA and IL17-AF assays, which represents one of the advantages associated with the compounds herein.

Compounds

Formula I

[0013] In some embodiments, the present disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

R¹ is an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Z is null, C(O), -C(O)-O-, or -C(O)-N(G^Z)-, wherein when Z is -C(O)-O-, or -C(O)-N(G^Z)-, the carbonyl group is bonded with the adjacent NH group in Formula I, and wherein G^Z is

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hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring;

R² is an optionally substituted carbocyclyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, or an optionally substituted alkyl;

Ring A is phenylene or 5- or 6-membered heteroarylene (e.g., pyridylene, pyridazinylene, pyrimidinylene, etc.), which is optionally substituted with 1-4 instances of R⁷ as valency permits;

R³ and R⁴ are each independently F, CN, G^{1A}, or J¹-J²-J³-G^{1B}, wherein J¹, J², and J³ are each independently null, O, NG^{1B}, C(O), S, SO, SO₂, or P(O)G^{1B}, provided that at least one of J¹, J², and J³ is not null, and wherein:

G^{1B} at each occurrence is independently hydrogen or G^{1A}, and

G^{1A} at each occurrence is independently an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring (preferably optionally substituted C₃₋₈ carbocyclic ring, or optionally substituted 4-8 membered heterocyclic ring);

or **R³ and R⁴**, together with the carbon atom they are both attached to, are joined to form an optionally substituted 3-8 membered carbocyclic or 4-8 membered heterocyclic ring;

L¹ is null, an optionally substituted C₁₋₄ alkylene, or an optionally substituted C₁₋₄ heteroalkylene,

R⁵ is hydrogen, deuterium, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, or optionally substituted 3-8 membered ring;

or either **R³ or R⁴**, together with **R⁵**, and the intervening atoms, are joined to form an optionally substituted 3-8 membered carbocyclic or 4-8 membered heterocyclic ring;

R⁶ is O-G^{2A}, N(G^{2A})C(O)G^{2A}, N(G^{2A})C(O)OG^{2B}, N(G^{2A})C(O)NG^{2A}G^{2A}, N(G^{2A})SO₂G^{2B}, or N(G^{2A})SO₂NG^{2A}G^{2A}, wherein G^{2A} at each occurrence is independently hydrogen or G^{2B}; and wherein G^{2B} at each occurrence is independently an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally

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substituted C₃₋₈ carbocyclic ring, optionally substituted 5- or 6-membered heteroaryl ring, or optionally substituted 4-8 membered heterocyclic ring),

Y is C(O) or SO₂;

R⁸ is NG³G³, an optionally substituted 4-14 membered heterocyclic ring, or an optionally substituted heteroaryl ring, wherein:

G³ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring; or two G³, together with the nitrogen atom they are both attached to, are joined to form an optionally substituted 4-8 membered heterocyclic ring;

R⁷ at each occurrence is independently deuterium, halogen, CN, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, optionally substituted 3-8 membered ring, or J⁴-J⁵-J⁶-G⁴, wherein J⁴, J⁵, and J⁶ are each independently null, O, NG⁴, C(O), S, SO, SO₂, or P(O)G⁴, wherein at least one of J⁴, J⁵, and J⁶ is not null, and wherein G⁴ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring; or two **R**⁷ can be joined to form an optionally substituted 4-8 membered ring;

or one instance of **R**⁷ and either **R**³ or **R**⁴, together with the intervening atoms, are joined to form an optionally substituted 5-8 membered carbocyclic or heterocyclic ring; and

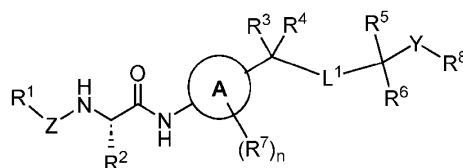
"**n**" is an integer selected from 0-4.

[0014] The compound of Formula I (including any of the applicable sub-formulae as described herein) comprises one or more asymmetric centers and/or axial chirality, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. In some embodiments, the compound of Formula I can exist in the form of an individual enantiomer and/or diastereomer, as applicable, or a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomers. In some embodiments, when applicable, the compound of Formula I (including any of the applicable sub-formulae as described herein) can exist as an individual enantiomer substantially free of the other enantiomer, such as having an enantiomeric excess ("ee") of greater than 60%, preferably, greater than 80% ee, greater than 90% ee, greater than 95% ee, greater than 98% ee, or greater than 99% ee. In

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some embodiments, when applicable, the compound of Formula I (including any of the applicable sub-formulae as described herein) can also exist as a mixture of stereoisomers in any ratio, such as a racemic mixture.

[0015] For example, in some embodiments, the compound of Formula I can be characterized as having a structure according to Formula I-E1:



Formula I-E1,

wherein the variables are defined herein. In some embodiments, the compound having a structure according to Formula I-E1 can exist as the as-drawn enantiomer substantially free of the other enantiomer with respect to the chiral carbon to which R² is attached, such as having an enantiomeric excess ("ee") of greater than 60%, preferably, greater than 80% ee, greater than 90% ee, greater than 95% ee, greater than 98% ee, or greater than 99% ee.

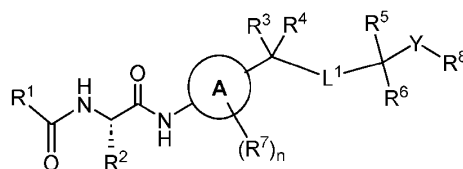
[0016] In some embodiments, the compound of Formula I (including any of the applicable sub-formulae as described herein) can exist as an isotopically labeled compound, particularly, a deuterated analog, wherein one or more of the hydrogen atoms of the compound of Formula I is/are substituted with a deuterium atom with an abundance above its natural abundance, e.g., a CD₃ analog when the compound has a CH₃ group. To be clear, when a substituent or a variable or other structures defined herein specifically refers to a deuterium, D, or deuterium containing group, it should be understood that the deuterium at each indicated position is greater than the natural abundance of deuterium (approximately 0.0156 mol%), for example, the indicated position(s) can have a deuterium content of at least 1 mol%, 10 mol%, 50 mol%, 90 mol%, 98 mol%, or 99 mol% deuterium. Without wishing to be bound by theories, it is believed that in certain situations, substitution with deuterium can lead to a deuterated analog with a better pharmacokinetic profile. Deuterated analogs can be generally prepared by using commercially available deuterating or deuterated reagents, which can typically have a high deuterium content, up to 99 mol% or above. In some embodiments, the compound of Formula I (including any of the applicable sub-formulae as described herein) exists as a non-isotopically labeled compound, in other words, all atoms in the compound have their

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respective natural abundances, for example, no hydrogen atom in the compound is substituted with a deuterium atom with an abundance above its natural abundance.

[0017] It should be apparent to those skilled in the art that in certain cases, the compound of Formula I may exist as a mixture of tautomers or atropisomers. The present disclosure is not limited to any specific tautomer or atropisomer. Rather, the present disclosure encompasses any and all of such tautomers or atropisomers whether or not explicitly drawn or referred to.

[0018] Typically, Z in Formula I or any of the applicable subformulae herein is C(O). For example, in preferred embodiments, the compound of Formula I can have a structure according to Formula I-A:



Formula I-A.

wherein the variables are defined herein.

[0019] In some embodiments, Z in Formula I or any of the applicable subformulae herein can

also be null, i.e., the moiety of $\text{R}^1\text{-Z-NH-}$ in Formula I is $\text{R}^1\text{-NH-}$. In some

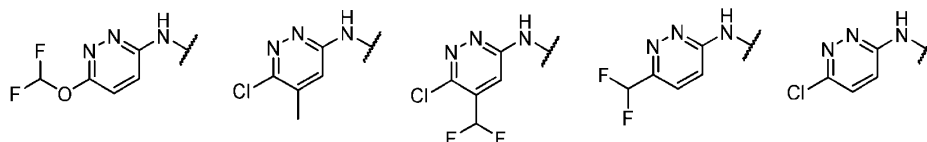
embodiments, the moiety of $\text{R}^1\text{-Z-NH-}$ in Formula I can be a heteroaryl amino group, i.e., Z

is null and R^1 is a heteroaryl, for example, in some embodiments, the moiety of $\text{R}^1\text{-Z-NH-}$ in Formula I is a 5 or 6-membered heteroaryl amino group, wherein the 5 or 6-membered heteroaryl ring is optionally substituted, for example, with 1 or 2 substituents each independently halogen, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the 5 or 6-membered heteroaryl ring can be selected from pyridine, pyridazine, pyrimidine, pyrazine, thiadiazole, oxadiazole, oxazole, imidazole, pyrazole, and isoxazole, which is optionally

substituted as described herein. In some specific embodiments, the moiety of $\text{R}^1\text{-Z-NH-}$ in Formula I can be a pyridazinyl amino group, wherein the pyridazine ring can be optionally substituted, such as with 1 or 2 substituents each independently halogen, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with

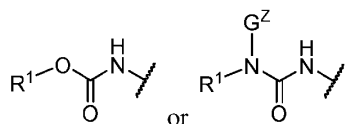
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deuterium and/or F, for example, the moiety of $\text{R}^1\text{-Z-NH}$ in Formula I can be selected from:



[0020] In some embodiments, Z in Formula I or any of the applicable subformulae herein can

also be -C(O)-O- or $\text{-C(O)-N(G}^{\text{Z}}\text{)-}$, and the moiety of $\text{R}^1\text{-Z-NH}$ in Formula I can be



. In some embodiments, G^{Z} can be hydrogen, C_{1-6} alkyl, or 3-5 membered ring, wherein the C_{1-6} alkyl or 3-5 membered ring can be unsubstituted or substituted with one or more substituents described herein, for example, suitable substituents can be oxo, halogen, C_{1-3} alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C_{1-3} alkyl, halogen, and/or OH. For example,

in some embodiments, the moiety of $\text{R}^1\text{-Z-NH}$ in Formula I can be $\text{R}^1\text{-O-C(=O)-NH}$, wherein R^1 is defined herein, such as a C_{3-10} carbocyclyl (e.g., cyclopropyl or cyclobutyl), which is optionally substituted with one or more substituents as described herein, for example, with one or more substituents independently selected from halogen, CN, OH, NH_2 , R^{A1} , OR^{A1} , SR^{A1} , NHR^{A1} , $\text{NR}^{\text{A1}}\text{R}^{\text{A1}}$, C(O)R^{A1} , $\text{C(O)NHR}^{\text{A1}}$, or $\text{C(O)NR}^{\text{A1}}\text{R}^{\text{A1}}$, wherein R^{A1} is defined herein.

[0021] Typically, R^1 in Formula I or any of the applicable subformulae herein is an optionally substituted heteroaryl. For example, in some preferred embodiments, R^1 in Formula I or any of the applicable subformulae herein is an optionally substituted 5- or 6-membered heteroaryl, more preferably, a substituted 5- or 6-membered heteroaryl. In some embodiments, R^1 is a 5- or 6-membered heteroaryl selected from pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, furan, thiophene, imidazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyrimidine, pyrazine, and pyridazine, each of which is optionally substituted. In some preferred embodiments, R^1 is a 5-membered heteroaryl, for example, a

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pyrazole (e.g., ) , isoxazole (e.g., ) , or oxadiazole (e.g., ) , which is optionally substituted. When substituted, the optionally substituted heteroaryl, such as the optionally substituted 5- or 6-membered heteroaryl, can be preferably substituted with one or more substituents as valency permits, with each substituent independently selected from halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, NR^{A1}SO₂R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, C(O)NR^{A1}R^{A1}, S(O)_qR^{A1}, S(O)_qNR^{A1}R^{A1}, and S(O)(=NR^{A1})R^{A1}

wherein:

q is 1 or 2; and

R^{A1} at each occurrence is independently C₁₋₆ alkyl, C₃₋₁₀ carbocyclic, or 4-10 membered heterocyclic ring, wherein:

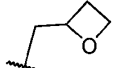
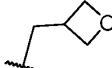
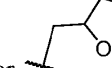
the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring (e.g., cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, etc.), wherein the C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH; and

the C₃₋₁₀ carbocyclic or 4-10 membered heterocyclic ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ alkyl, C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH.

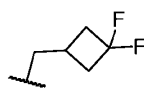
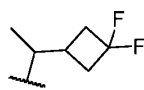
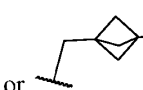
In some preferred embodiments, R^{A1} at each occurrence is independently (1) C₁₋₄ alkyl optionally substituted with one or more substituents independently selected from deuterium, F, and OH, or (2) a C₃₋₆ cycloalkyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH, or (3) a 4-6 membered heterocyclyl optionally substituted with one or more substituents

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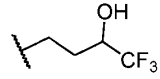
independently selected from deuterium, methyl, F, and OH; or (4) (C₁₋₃ alkylene)-(3-6 membered ring), wherein the C₁₋₃ alkylene and 3-6 membered ring are each independently optionally substituted with one or more substituents independently selected from deuterium, methyl, CD₃, F, and OH, wherein the 3-6 membered ring is a C₃₋₆ cycloalkyl or 4-6 membered heterocyclyl, for example, one R^{A1} can be cyclopropylmethyl,

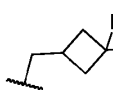
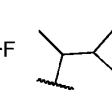
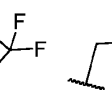
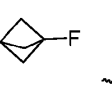
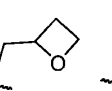
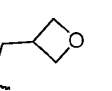
cyclobutylmethyl, , , or . In some preferred

embodiments, R^{A1} at each occurrence is independently (i) C₁₋₄ alkyl optionally substituted with deuterium and/or F, e.g., methyl, CD₃, ethyl, CD₂CD₃, isopropyl, difluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or 2,2-difluoroethyl; (ii) (C₁₋₂ alkylene)-C₃₋₅ cycloalkyl, such as cyclopropylmethyl, wherein the C₁₋₂ alkylene and C₃₋₅ cycloalkyl are each independently optionally substituted with methyl, deuterium, and/or F; for example, one

R^{A1} is , , or ; or (iii) C₃₋₄ cycloalkyl optionally

substituted with methyl and/or F. In some preferred embodiments, R^{A1} at each occurrence is independently C₁₋₄ alkyl optionally substituted with deuterium and/or F or C₃₋₄ cycloalkyl optionally substituted with F. In some specific embodiments, R^{A1} at each occurrence is independently methyl, CD₃, ethyl, isopropyl, difluoromethyl, 2,2-difluoroethyl, cyclopropylmethyl, or cyclopropyl. In some specific embodiments, R^{A1} at each occurrence is independently methyl, CD₃, ethyl, CD₂CD₃, isopropyl, difluoromethyl,

2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, , cyclopropylmethyl,

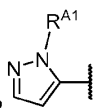
cyclobutylmethyl, , , , , , , or cyclopropyl.

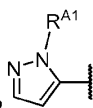
[0022] In some embodiments, R¹ in Formula I or any of the applicable subformulae herein can be a 5- or 6-membered heteroaryl selected from pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, furan, thiophene, imidazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyrimidine, pyrazine, and pyridazine, which is unsubstituted or substituted with 1 or 2 substituents independently selected from halogen, CN, R^{A1}, or OR^{A1}, wherein R^{A1} is

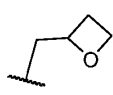
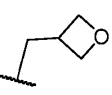
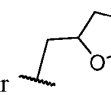
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defined and preferred herein. In some embodiments, R^1 in Formula I or any of the applicable subformulae herein can be a 5-membered heteroaryl selected from pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, furan, thiophene, imidazole, oxadiazole, thiadiazole, triazole, or tetrazole, which is unsubstituted or substituted with 1 or 2 independently selected R^{A1} , wherein R^{A1} is defined and preferred herein. Although readily apparent, to be further clear, when it is said that a variable of Formula I or any of the applicable subformulae herein has a recited definition, it is to be understood that such applicable subformulae include any of the subformulae of Formula I herein that does not define the variable contradictory to the recited definition.

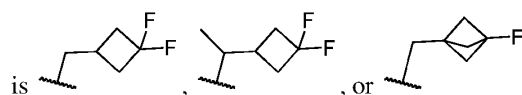
[0023] In some preferred embodiments, R^1 in Formula I or any of the applicable subformulae

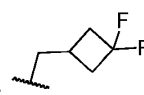
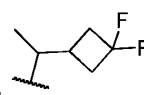
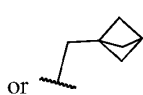


herein can have a structure according to , wherein R^{A1} is defined and preferred herein. For example, in some embodiments, R^{A1} can be (1) a C_{1-4} alkyl optionally substituted with one or more substituents independently selected from deuterium, F, and OH, or (2) a C_{3-6} cycloalkyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH; (3) a 4-6 membered heterocyclyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH; or (4) $(C_{1-3} \text{ alkylene})-(3-6 \text{ membered ring})$, wherein the C_{1-3} alkylene and 3-6 membered ring are each independently optionally substituted with one or more substituents independently selected from deuterium, methyl, CD_3 , F, and OH, wherein the 3-6 membered ring is a C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, for example, R^{A1} can be cyclopropylmethyl,

cyclobutylmethyl, , , or . In some embodiments, R^{A1} can be

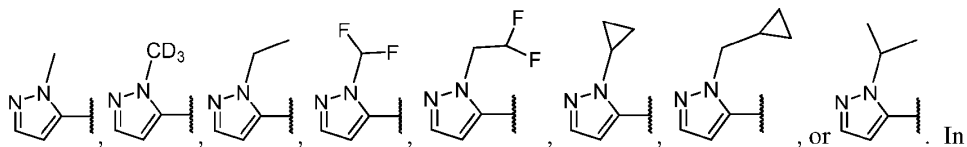
(i) C_{1-4} alkyl optionally substituted with deuterium and/or F, e.g., methyl, CD_3 , ethyl, isopropyl, difluoromethyl, 2,2-difluoroethyl; (ii) $(C_{1-2} \text{ alkylene})-C_{3-5}$ cycloalkyl, such as cyclopropylmethyl, cyclobutylmethyl, etc., wherein the C_{1-2} alkylene and C_{3-5} cycloalkyl are each independently optionally substituted with methyl, deuterium, and/or F; for example, R^{A1}



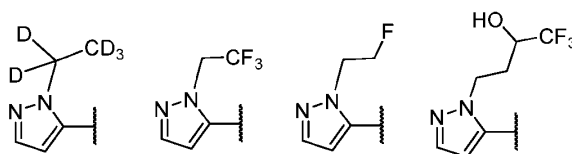
is , , or ; or (iii) C_{3-4} cycloalkyl optionally substituted with methyl and/or F. In some embodiments, R^{A1} can be C_{1-4} alkyl optionally substituted with deuterium and/or F or C_{3-4} cycloalkyl optionally substituted with F. In some

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specific embodiments, R^1 in Formula I or any of the applicable subformulae herein can be

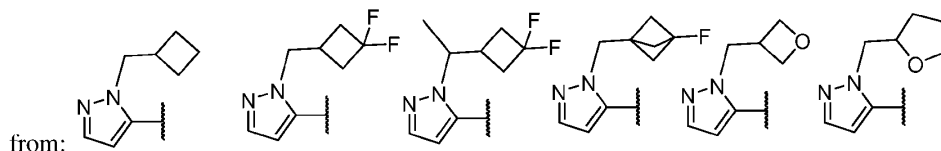


some specific embodiments, R^1 in Formula I or any of the applicable subformulae herein can



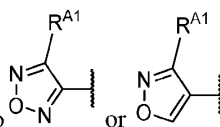
be selected from: . In some specific

embodiments, R^1 in Formula I or any of the applicable subformulae herein can be selected

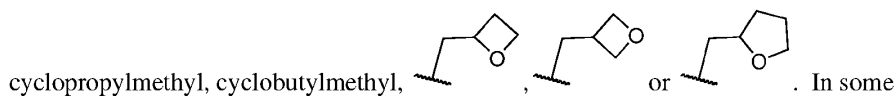


from:

[0024] In some preferred embodiments, R^1 in Formula I or any of the applicable subformulae



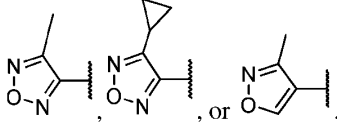
herein can have a structure according to , wherein R^{A1} is defined and preferred herein. For example, in some embodiments, R^{A1} can be (1) a C_{1-4} alkyl optionally substituted with one or more substituents independently selected from deuterium, F, and OH, (2) a C_{3-6} cycloalkyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH, (3) a 4-6 membered heterocyclyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH; or (4) (C_{1-3} alkylene)-(3-6 membered ring), wherein the C_{1-3} alkylene and 3-6 membered ring are each independently optionally substituted with one or more substituents independently selected from deuterium, methyl, CD_3 , F, and OH, wherein the 3-6 membered ring is a C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, for example, R^{A1} can be



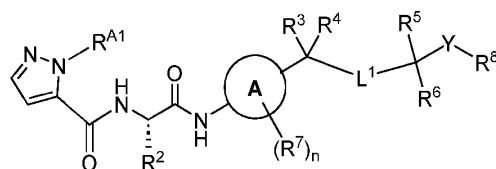
embodiments, R^{A1} can be (i) C_{1-4} alkyl optionally substituted with deuterium and/or F, (ii) (C_{1-2} alkylene)- C_{3-5} cycloalkyl, such as cyclopropylmethyl, wherein the C_{1-2} alkylene and C_{3-5}

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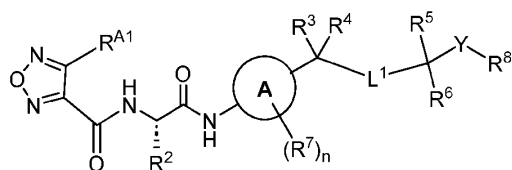
cycloalkyl are each independently optionally substituted with methyl, deuterium, and/or F; or (iii) C₃₋₄ cycloalkyl optionally substituted with methyl and/or F. In some embodiments, R^{A1} can be C₁₋₄ alkyl optionally substituted with deuterium and/or F or C₃₋₄ cycloalkyl optionally substituted with F. In some more specific embodiments, R¹ in Formula I or any of the

applicable subformulae herein can be .

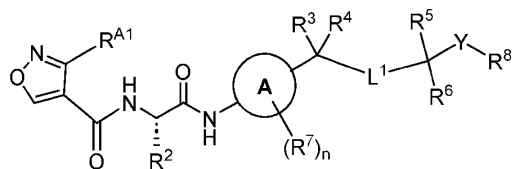
[0025] In some embodiments, the compound of Formula I can be characterized as having a structure according to Formula I-A1, I-A2, I-A3:



Formula I-A1,



Formula I-A2,

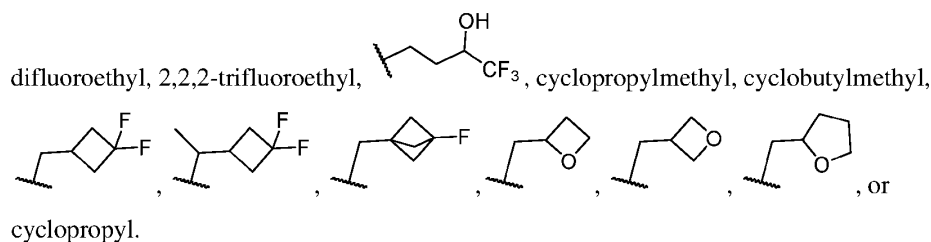


Formula I-A3,

wherein the variables are defined herein. For example, in some embodiments, R^{A1} in Formula I-A1, I-A2, or I-A3 can be a C₁₋₄ alkyl optionally substituted with one or more substituents independently selected from deuterium, F, and OH, or a C₃₋₆ cycloalkyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH. In some embodiments, R^{A1} in Formula I-A1, I-A2, or I-A3 can be (i) C₁₋₄ alkyl optionally substituted with deuterium and/or F, e.g., methyl, CD₃, ethyl, isopropyl, difluoromethyl, 2,2-difluoroethyl; (ii) (C₁₋₂ alkylene)-C₃₋₅ cycloalkyl, such as cyclopropylmethyl, wherein the C₁₋₂ alkylene and C₃₋₅ cycloalkyl are each independently

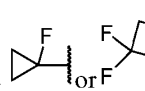
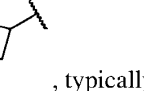
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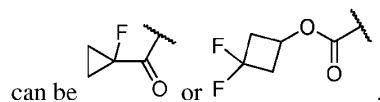
optionally substituted with methyl, deuterium, and/or F; or (iii) C₃₋₄ cycloalkyl optionally substituted with methyl and/or F. In some embodiments, R^{A1} in Formula I-A1, I-A2, or I-A3 can be a C₁₋₄ alkyl optionally substituted with deuterium and/or F or C₃₋₄ cycloalkyl optionally substituted with F. In some more specific embodiments, R^{A1} in Formula I-A1, I-A2, or I-A3 can be methyl, CD₃, ethyl, isopropyl, difluoromethyl, 2,2-difluoroethyl, cyclopropylmethyl, or cyclopropyl. In some specific embodiments, R^{A1} in Formula I-A1, I-A2, or I-A3 is methyl, CD₃, ethyl, CD₂CD₃, isopropyl, difluoromethyl, 2-fluoroethyl, 2,2-



[0026] In some embodiments, R¹ in Formula I or any of the applicable subformulae herein can also be a C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, optionally substituted with one or more substituents as described herein, for example, with one or more substituents independently selected from halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, or C(O)NR^{A1}R^{A1}, wherein R^{A1} is defined herein.

[0027] In some embodiments, R¹ in Formula I or any of the applicable subformulae herein can also be a carbocyclyl, such as a C₃₋₁₀ carbocyclyl (e.g., cyclopropyl or cyclobutyl), which is optionally substituted with one or more substituents as described herein, for example, with one or more substituents independently selected from halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, or C(O)NR^{A1}R^{A1}, wherein R^{A1} is defined

herein. For example, in some embodiments, R¹ can be  or , typically, in such embodiments, Z is C(O) or -C(O)-O-. For example, in some embodiments, Z-R¹ in Formula I



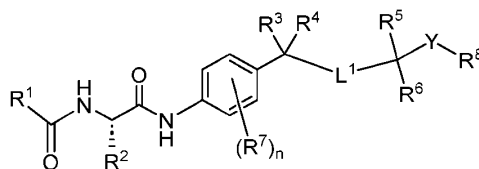
[0028] In some embodiments, R¹ in Formula I or any of the applicable subformulae herein can also be a heterocyclyl, such as a 4-10 membered heterocyclyl having 1-3 ring heteroatoms independently selected from O, N, and S, which is optionally substituted with one or more substituents as described herein, for example, with one or more substituents

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independently selected from halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, or C(O)NR^{A1}R^{A1}, wherein R^{A1} is defined herein.

[0029] In some embodiments, R¹ in Formula I or any of the applicable subformulae herein can also be an aryl, such as a phenyl, which is optionally substituted with one or more substituents as described herein, for example, with one or more substituents independently selected from halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, or C(O)NR^{A1}R^{A1}, wherein R^{A1} is defined herein.

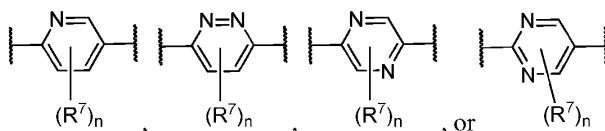
[0030] In Formula I (or any of the applicable subformulae herein, e.g., I-A, I-A1, I-A2, or I-A3), Ring A is typically a phenylene, optionally substituted with 1-4 R⁷, i.e., n is 0-4. For example, in some preferred embodiments, the compound of Formula I can be characterized as having a structure according to Formula I-1:



Formula I-1,

wherein the variables are defined herein.

[0031] In some embodiments, in Formula I (e.g., any of the applicable subformulae, e.g., I-A, I-A1, I-A2, or I-A3), Ring A is a 6-membered heteroarylene (e.g., pyridylene, pyridazinylene, pyrazinylene, pyrimidinylene, etc.). For example, in some embodiments, Ring A and (R⁷)_n

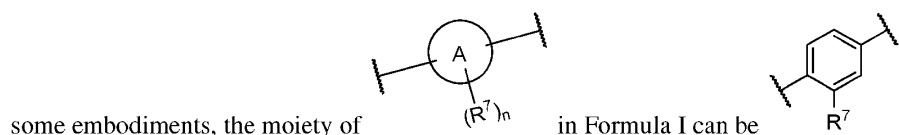


together can have a structure of (R⁷)_n, (R⁷)_n, (R⁷)_n, or (R⁷)_n, wherein n is 0-3 as valency permits and R⁷ are as defined herein.

[0032] The integer n in Formula I can range from 0-4, typically, 0, 1, or 2.

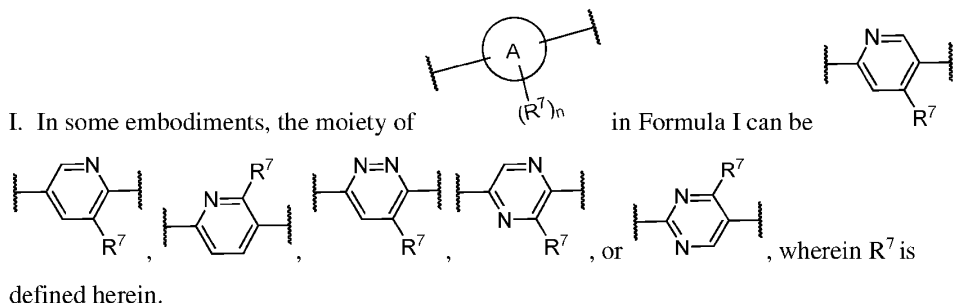
[0033] In some embodiments, in Formula I (e.g., any of the applicable subformulae, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc.), the integer n can be 0.

[0034] In some embodiments, in Formula I (e.g., any of the applicable subformulae, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc.), the integer n can be 1. For example, in



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wherein R^7 is defined herein, preferably, R^7 is ortho to the $NHC(O)$ moiety drawn in Formula



[0035] In some embodiments, in Formula I (e.g., any of the applicable subformulae, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc.), the integer n can also be greater than 1, such as 2 or 3, as valency permits.

[0036] In some embodiments, in Formula I (e.g., any of the applicable subformulae, e.g., I-A, I-A1, I-A2, or I-A3), Ring A can also be a 5-membered heteroarylene.

[0037] Typically, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^2 is an optionally substituted 3-14 membered carbocyclyl, which is monocyclic or polycyclic (including bicyclic, tricyclic, etc.). When substituted, the 3-14 membered carbocyclyl is preferably substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2} , SR^{A2} , $NR^{A2}R^{A2}$, $C(O)R^{A2}$, $C(O)OR^{A2}$, $C(O)NR^{A2}R^{A2}$, $S(O)R^{A2}$, SO_2R^{A2} , $SO_2NR^{A2}R^{A2}$, $OC(O)R^{A2}$, $NR^{A2}C(O)R^{A2}$, $NR^{A2}SO_2R^{A2}$, $PO(R^{A2})(R^{A2})$, or R^{B2} ,

wherein R^{A2} at each occurrence is independently hydrogen or R^{B2} , and

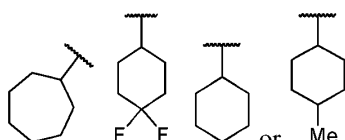
wherein R^{B2} at each occurrence is independently an optionally substituted group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or a 3-7 membered carbocyclic or 4-7 membered heterocyclic ring, wherein, when substituted,

the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C_{1-3} alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C_{1-3} alkyl, halogen, and/or OH; and

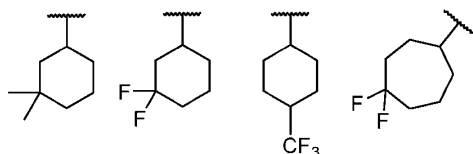
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the 3-7 membered carbocyclic or 4-7 membered heterocyclic ring is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ alkyl, C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH.

[0038] For example, in some preferred embodiments, R² is an optionally substituted monocyclic C₃₋₈ cycloalkyl, for example, a monocyclic C₃₋₈ cycloalkyl optionally substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2}, SR^{A2}, NR^{A2}R^{A2}, C(O)R^{A2}, C(O)OR^{A2}, C(O)NR^{A2}R^{A2}, S(O)R^{A2}, SO₂R^{A2}, SO₂NR^{A2}R^{A2}, OC(O)R^{A2}, NR^{A2}C(O)R^{A2}, NR^{A2}SO₂R^{A2}, PO(R^{A2})(R^{A2}), or R^{B2}, wherein R^{A2} and R^{B2} are defined herein. In some preferred embodiments, when substituted, the monocyclic C₃₋₈ cycloalkyl can be substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F. In some embodiments, R² is an unsubstituted monocyclic C₃₋₈ cycloalkyl, such as cyclopentyl, cyclohexyl, or cycloheptyl. In some embodiments, R² is a monocyclic C₃₋₇ cycloalkyl, such as cyclohexyl or cycloheptyl, which is optionally substituted with one or more substituents each independently deuterium, F, or C₁₋₃ alkyl optionally substituted with one or more G^{S2}, wherein G^{S2} at each occurrence is independently deuterium, F, or OH. In some preferred embodiments, G^{S1} or G^{S2} can be F. In some embodiments, R² is a monocyclic C₃₋₇ cycloalkyl, optionally substituted with one or more (e.g., 1 or 2) methyl. In some embodiments, R² is a monocyclic C₃₋₇ cycloalkyl, optionally substituted with one or more (e.g., 1 or 2) F. In some embodiments, R² is a monocyclic C₃₋₇ cycloalkyl, optionally substituted with one or more (e.g., 1) CF₃. In some

embodiments, R² is . In some embodiments, R² is selected

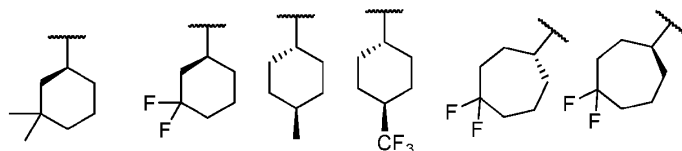
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from the following:

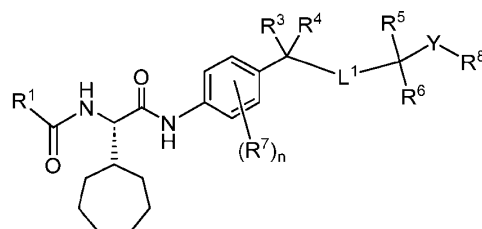
. In some embodiments, R^2

is selected from the following:



. For example, in some

specific embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1a:

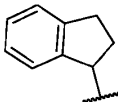
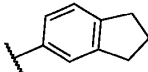


Formula I-1a,

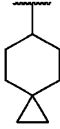
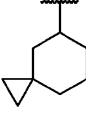
wherein the variables are defined herein.

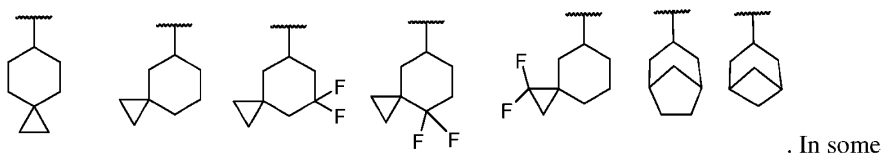
[0039] In some embodiments, R^2 can also be an optionally substituted polycyclic C_{4-10} carbocyclyl, e.g., spiro [2,5] octanyl, indanyl, etc., for example, a polycyclic C_{4-10} carbocyclyl optionally substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2} , SR^{A2} , $NR^{A2}R^{A2}$, $C(O)R^{A2}$, $C(O)OR^{A2}$, $C(O)NR^{A2}R^{A2}$, $S(O)R^{A2}$, SO_2R^{A2} , $SO_2NR^{A2}R^{A2}$, $OC(O)R^{A2}$, $NR^{A2}C(O)R^{A2}$, $NR^{A2}SO_2R^{A2}$, $PO(R^{A2})(R^{A2})$, or R^{B2} , wherein R^{A2} and R^{B2} are defined herein. In some preferred embodiments, when substituted, the polycyclic C_{4-10} carbocyclyl can be substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} alkoxy optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. To be clear, the polycyclic C_{4-10} carbocyclyl herein includes ring systems in which one of the rings is an aromatic ring, so long as the ring system as a whole is

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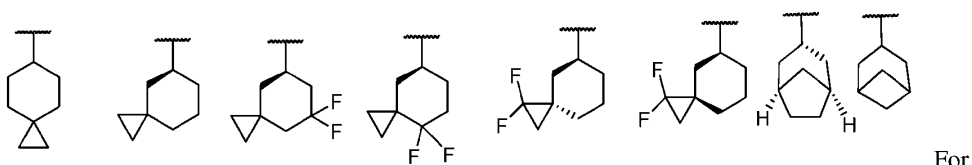
non-aromatic. For example, both  and  are examples of unsubstituted C₉ carbocyclyl groups.

[0040] In some embodiments, R² can be a spiro, fused, or bridged bicyclic C₄₋₁₀ cycloalkyl,

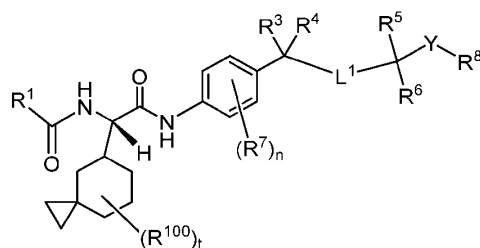
e.g.,  or , which is optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F. For example, in some embodiments, R² is selected from:



embodiments, R² is selected from:



example, in some preferred embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1c:

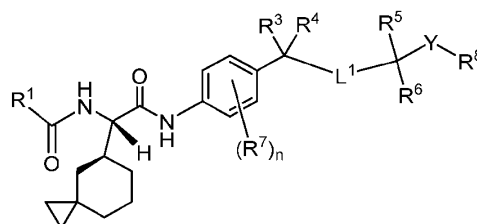


Formula I-1c,

wherein t is 0, 1, or 2, and R¹⁰⁰ at each occurrence is independently halogen, C₁₋₃ alkyl optionally substituted with deuterium or F, or C₁₋₃ alkoxy optionally substituted with

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deuterium or F, and the other variables are defined herein. In Formula I-1c, when t is not 0, R^{100} should be understood as a substituent of either the cyclohexyl or cyclopropyl portion of the bicyclic structure. In some embodiments, t is 0. In some embodiments, t is 2. In some embodiments, R^{100} at each occurrence is F. In some preferred embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1c-1:



Formula I-1c-1,

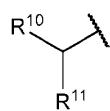
wherein the variables are defined herein.

[0041] In some preferred embodiments, R^2 in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., can be an optionally substituted alkyl. Preferably, in such embodiments, R^2 in Formula I or any of the applicable subformulae herein can be a substituted methyl group, in which one or two hydrogen atoms are independently substituted with an alkyl, heteroalkyl, or a 3-12 membered ring structure (e.g., a monocyclic ring selected from C_{3-7} carbocyclic, a 4-8 membered heterocyclic, phenyl, or 5 or 6 membered heteroaryl; or a spiro, fused, or bridged 5-12 membered bicyclic ring in which each ring is independently a carbocyclic, heterocyclic, phenyl, or 5 or 6 membered heteroaryl), each of which is further optionally substituted. In some embodiments, the substituted methyl group is substituted with two independently selected optionally substituted 3-12 membered ring structures selected from (1) a monocyclic ring selected from C_{3-7} carbocyclic, 4-8 membered heterocyclic, phenyl, or 5 or 6 membered heteroaryl; or (2) a spiro, fused, or bridged 5-12 membered bicyclic ring in which each ring is independently a carbocyclic, heterocyclic, phenyl, or 5 or 6 membered heteroaryl. In some embodiments, the substituted methyl group is substituted with one substituent which is an optionally substituted 3-12 membered ring structure selected from (1) a monocyclic ring selected from C_{3-7} carbocyclic, a 4-8 membered heterocyclic, phenyl, or 5 or 6 membered heteroaryl; or (2) a spiro, fused, or bridged 5-12 membered bicyclic ring in which each ring is independently a carbocyclic, heterocyclic, phenyl, or 5 or 6 membered heteroaryl; and optionally another substituent which is an optionally substituted alkyl or heteroalkyl. When substituted, the

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optionally substituted 3-12 membered ring structure or the optionally substituted alkyl or heteroalkyl is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, or an optionally substituted 3-7 membered ring structure (e.g., carbocyclic, heterocyclic, phenyl, or heteroaryl), wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, wherein the optionally substituted 3-7 membered ring structure is optionally substituted with one or more substituents each independently deuterium, halogen, CN, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, or cyclopropyl or cyclobutyl optionally substituted with deuterium, F, OH, and/or methyl.

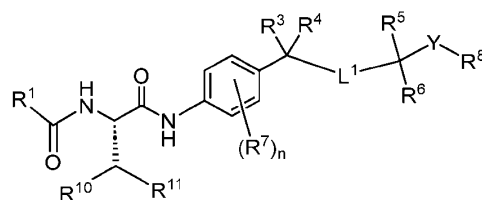
[0042] In some preferred embodiments, R² in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., can have a structure of



, wherein R¹⁰ and R¹¹ are each independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted C₃₋₇ carbocyclic, or optionally substituted phenyl, wherein at least one of R¹⁰ and R¹¹ is not hydrogen, preferably, both of R¹⁰ and R¹¹ are not hydrogen. R¹⁰ and R¹¹ can be the same or different. When substituted, the optionally substituted group for R¹⁰ or R¹¹ can be preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, or an optionally substituted 3-7 membered ring structure (e.g., carbocyclic, heterocyclic, phenyl, or heteroaryl), wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, wherein the optionally substituted 3-7 membered ring structure is optionally substituted with one or more substituents each independently deuterium, halogen, CN, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F, or cyclopropyl or cyclobutyl optionally substituted with deuterium, F, OH, and/or methyl.

[0043] In some specific embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1b:

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Formula I-1b,

wherein the variables are defined herein.

[0044] In some embodiments, R^{10} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0045] In some embodiments, R^{10} is (1) a C_{3-6} cycloalkyl; or (2) $-(C_{1-3} \text{ alkylene})-(C_{3-6} \text{ cycloalkyl})$, wherein each of the C_{1-3} alkylene and C_{3-6} cycloalkyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the C_{1-3} alkylene is unsubstituted. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the C_{3-6} cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from F and C_{1-3} alkyl optionally substituted with F. For example, in some preferred embodiments, R^{10} is cyclopropyl, methylcyclopropyl, or cyclobutyl.

[0046] In some embodiments, R^{10} is (1) a phenyl; or (2) $-(C_{1-3} \text{ alkylene})\text{-phenyl}$, wherein each of the C_{1-3} alkylene and phenyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the C_{1-3} alkylene is unsubstituted. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the phenyl is unsubstituted or substituted with one or more substituents independently selected from halogen (e.g., F or Cl), and C_{1-3} alkyl optionally substituted with F. For example, in some preferred embodiments, R^{10} is phenyl. In some embodiments, R^{10} is substituted phenyl, e.g., halogen substituted phenyl, such as phenyl substituted with one or two halogens independently selected from F and Cl.

[0047] In some embodiments, R^{11} is (1) a C_{3-6} cycloalkyl; or (2) $-(C_{1-3} \text{ alkylene})-(C_{3-6} \text{ cycloalkyl})$, wherein each of the C_{1-3} alkylene and C_{3-6} cycloalkyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the C_{1-3} alkylene is unsubstituted. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the C_{3-6} cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from F and C_{1-3} alkyl optionally substituted with F. For example, in some preferred embodiments, R^{11} is cyclopropyl, methylcyclopropyl, or cyclobutyl.

[0048] In some embodiments, R^{11} is (1) a phenyl; or (2) $-(C_{1-3} \text{ alkylene})\text{-phenyl}$, wherein each of the C_{1-3} alkylene and phenyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the C_{1-3} alkylene is unsubstituted. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the phenyl is unsubstituted or substituted with one or more substituents independently selected from halogen (e.g., F or Cl), and C_{1-3} alkyl optionally substituted with F. For example, in some preferred embodiments, R^{11} is phenyl. In some embodiments, R^{11} is substituted phenyl, e.g., halogen substituted phenyl, such as phenyl substituted with one or two halogens independently selected from F and Cl.

[0049] In some embodiments, R^{10} and R^{11} are independently a C_{3-6} cycloalkyl, which is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the C_{3-6} cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from F and C_{1-3} alkyl optionally substituted with F.

[0050] In some embodiments, R^{10} and R^{11} are independently a phenyl, which is optionally substituted, for example, with one or more substituents each independently deuterium,

halogen, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the phenyl is unsubstituted or substituted with one or more substituents independently selected from halogen (e.g., F or Cl), and C₁₋₃ alkyl optionally substituted with F. In some embodiments, the phenyl is unsubstituted or substituted with halogen, such as phenyl substituted with one or two halogens independently selected from F and Cl.

[0051] In some embodiments, R¹⁰ is a C₃₋₆ cycloalkyl and R¹¹ is a phenyl, wherein the C₃₋₆ cycloalkyl and phenyl is independently optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, the C₃₋₆ cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from F and C₁₋₃ alkyl optionally substituted with F. In some embodiments, the phenyl is unsubstituted or substituted with one or more substituents independently selected from halogen (e.g., F or Cl), and C₁₋₃ alkyl optionally substituted with F. In some embodiments, the phenyl is unsubstituted or substituted with halogen, such as phenyl substituted with one or two halogens independently selected from F and Cl.

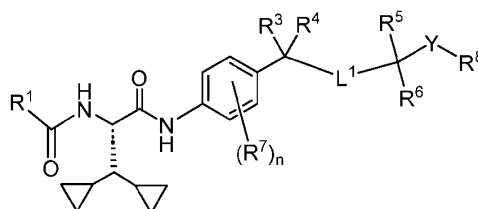
[0052] In some embodiments, R¹⁰ is an optionally substituted C₁₋₄ alkyl, e.g., C₁₋₄ alkyl optionally substituted with one or more G^{S1}, and R¹¹ is a C₃₋₆ cycloalkyl or phenyl, wherein the C₃₋₆ cycloalkyl and phenyl is independently optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, CN, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F. In some embodiments, G^{S1} at each occurrence is F. In some embodiments, R¹¹ is a C₃₋₆ cycloalkyl and the C₃₋₆ cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from F and C₁₋₃ alkyl optionally substituted with F. In some embodiments, R¹¹ is a phenyl and the phenyl

is unsubstituted or substituted with one or more substituents independently selected from halogen (e.g., F or Cl), and C₁₋₃ alkyl optionally substituted with F.

[0053] In some embodiments, R¹⁰ and R¹¹ are independently selected from cyclopropyl, methylcyclopropyl, cyclobutyl, phenyl, and phenyl substituted with one or two halogens independently selected from F and Cl.

[0054] In some embodiments, R¹⁰ and R¹¹ are the same. For example, in some embodiments, both R¹⁰ and R¹¹ are cyclopropyl. In some embodiments, both R¹⁰ and R¹¹ are cyclobutyl. In some embodiments, both R¹⁰ and R¹¹ are phenyl.

[0055] In some specific embodiments, the compound of Formula I-1b can be characterized as having a structure according to Formula I-1b-1:



Formula I-1b-1,

wherein the variables are defined herein.

[0056] In some embodiments, R^{10} and R^{11} are different.

[0057] In some embodiments, R² in Formula I or any of the applicable subformulae herein can also be an optionally substituted heterocyclyl, which includes monocyclic heterocyclyl or polycyclic heterocyclyl. To be clear, a polycyclic heterocyclic ring herein can have two or more rings, in which one or more of the rings can be a phenyl or heteroaryl ring, or a carbocyclic ring, so long as the ring system overall is not aromatic and contains at least one ring heteroatom. For example, a polycyclic heterocyclyl can be a ring selected from fused heteroarylcyaloalkyl, fused heteroarylheterocycloalkyl, fused arylheterocycloalkyl, and tricyclic ring system such as spirochromanes.

[0058] In some preferred embodiments, R² in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., can be an optionally substituted 10-14 membered polycyclic heterocyclyl having 1-3 ring heteroatoms independently selected from S, O, and N, and wherein when substituted, the 10-14 membered polycyclic heterocyclyl is preferably substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2}, SR^{A2}, NR^{A2}R^{A2}, C(O)R^{A2}, C(O)OR^{A2},

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$C(O)NR^{A2}R^{A2}$, $S(O)R^{A2}$, SO_2R^{A2} , $SO_2NR^{A2}R^{A2}$, $OC(O)R^{A2}$, $NR^{A2}C(O)R^{A2}$, $NR^{A2}SO_2R^{A2}$, $PO(R^{A2})(R^{A2})$, or R^{B2} ,

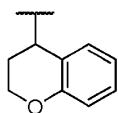
wherein R^{A2} at each occurrence is independently hydrogen or R^{B2} , and

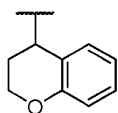
wherein R^{B2} at each occurrence is independently an optionally substituted group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or a 3-7 membered carbocyclic or 4-7 membered heterocyclic ring, wherein, when substituted,

the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C_{1-3} alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C_{1-3} alkyl, halogen, and/or OH; and

the 3-7 membered carbocyclic or 4-7 membered heterocyclic ring is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C_{1-3} alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C_{1-3} alkyl, halogen, and/or OH.

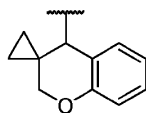
In some embodiments, the 10-14 membered polycyclic heterocyclyl having 1-3 ring heteroatoms independently selected from S, O, and N, is optionally substituted with one or more substituents each independently halogen, CN, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, the 10-14 membered polycyclic heterocyclyl has a fused ring structure from a 5-7 membered heterocyclic ring and a phenyl or 6-membered heteroaryl ring, and optionally one additional ring which forms a spiro, fused, or bridged structure with the 5-7 membered heterocyclic ring. For example, in some embodiments, the 10-14 membered polycyclic heterocyclyl is a bicyclic fused ring from a 6-membered heterocyclic ring (e.g., a 6-membered heterocyclic ring having one ring heteroatom which is O, N, or S) and a phenyl



ring, such as , which is optionally substituted as defined herein. To be clear, when

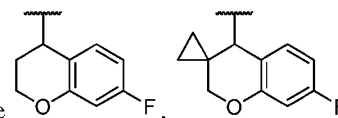
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substituted, the substitution can occur on either the phenyl ring portion or the dihydropyran portion; unless otherwise specified or contrary from context, allowable substitutions for other optionally substituted polycyclic rings herein should be understood similarly. In some embodiments, the 10-14 membered polycyclic heterocyclyl has a bicyclic fused ring from a 6-membered heterocyclic ring having one heteroatom which is O, N, or S, and a phenyl ring, optionally also contains a spiro cyclopropyl ring to the 6 membered heterocyclic ring, i.e., the spiro cyclopropyl ring, if exists, shares one carbon atom with the 6-membered heterocyclic ring. In some embodiments, the 10-14 membered polycyclic heterocyclyl has a bicyclic fused ring from a 6-membered heterocyclic ring having one heteroatom which is O, N, or S, and a phenyl ring, and a spiro cyclopropyl ring that shares one carbon atom with the 6-membered heterocyclic ring. For example, in some embodiments, the 10-14 membered

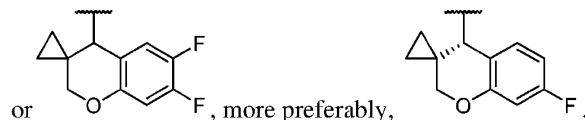


polycyclic heterocyclyl is , which is optionally substituted as defined herein.

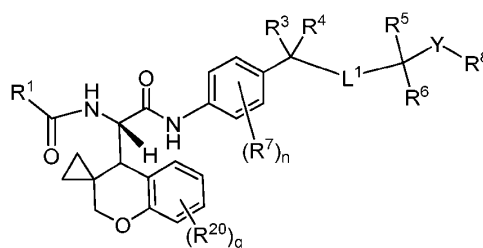
In some embodiments, R^2 in Formula I or any of the applicable subformulae herein, such as



Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., can be



[0059] In some preferred embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1d:

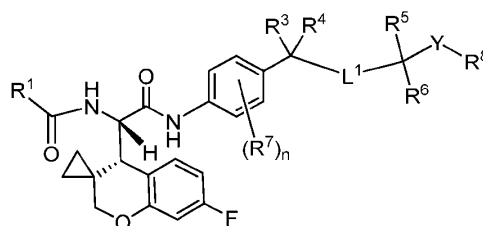


Formula I-1d,

wherein q is 0, 1, or 2, and R^{20} at each occurrence is independently halogen, C_{1-3} alkyl optionally substituted with deuterium or F, or C_{1-3} alkoxy optionally substituted with deuterium or F, and the other variables are defined herein. In Formula I-1d, when q is not 0,

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R^{20} should be understood as a substituent of the phenyl ring portion of the tricyclic structure. In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments q is 2. In some embodiments, R^{20} at each occurrence is F. In some embodiments, the compound of Formula I-1 can be characterized as having a structure according to Formula I-1d-1:



Formula I-1d-1,

wherein the variables are defined herein.

[0060] In some embodiments, in Formula I or any of the applicable subformulae herein, R^3 and R^4 are independently G^{1A} . In some embodiments, one of R^3 and R^4 is G^{1A} , and the other of R^3 and R^4 is represented by the general formula J^1 - J^2 - J^3 - G^{1B} as defined herein. The combination of J^1 , J^2 , and J^3 is not particularly limited, which can preferably be (a) a linker of O, NG^{1B} , C(O), S, SO, SO_2 , or $P(O)G^{1B}$, when two of J^1 , J^2 , and J^3 are null, or (b) a linker of amide (C(O) NG^{1B}), ester (C(O)O), sulfonamide (SO_2NG^{1B}), etc., when one of J^1 , J^2 , and J^3 is null, or (c) a linker of carbamate (OC(O) NG^{1B}), urea ($NG^{1B}C(O)NG^{1B}$), sulfamoylamino ($NG^{1B}SO_2NG^{1B}$), etc., when none of J^1 , J^2 , and J^3 is null.

[0061] In some embodiments, in Formula I or any of the applicable subformulae herein, R^3 and R^4 are each independently C_{1-4} alkyl optionally substituted with one or more G^{S2} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S2} , wherein G^{S2} at each occurrence is independently deuterium, F, or OH. In some embodiments, G^{S2} at each occurrence is F.

[0062] In some embodiments, R^3 is C_{1-4} alkyl optionally substituted with deuterium and/or F. For example, in some embodiments, R^3 is an unsubstituted C_{1-4} alkyl or a C_{1-4} alkyl substituted with one or more (e.g., 1, 2, or 3) F. For example, in some embodiments, R^3 can be methyl.

[0063] In some embodiments, R^4 is C_{1-4} alkyl optionally substituted with deuterium and/or F. For example, in some embodiments, R^4 is an unsubstituted C_{1-4} alkyl or a C_{1-4} alkyl substituted with one or more (e.g., 1, 2, or 3) F, for example, R^4 is methyl.

[0064] In some embodiments, R^4 is a C_{3-6} cycloalkyl or $-(C_{1-3} \text{ alkylene})-(C_{3-6} \text{ cycloalkyl})$, wherein each of the C_{3-6} cycloalkyl is optionally substituted with one or more substituents

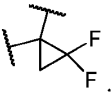
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each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F.

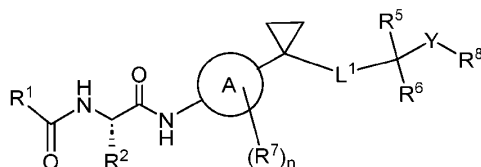
[0065] In some embodiments, both R³ and R⁴ are independently selected from C₁₋₄ alkyl optionally substituted with deuterium and/or F. For example, in some embodiments, both R³ and R⁴ are independently an unsubstituted C₁₋₄ alkyl or a C₁₋₄ alkyl substituted with one or more (e.g., 1, 2, or 3) F. For example, in some embodiments, both R³ and R⁴ can be methyl.

[0066] In some preferred embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R³ and R⁴, together with the carbon atom they are both attached to, are joined to form a 3-7 membered carbocyclic ring, which is optionally substituted. For example, in some preferred embodiments, R³ and R⁴, together with the carbon atom they are both attached to, are joined to form an optionally

substituted cyclopropyl ring, for example, an unsubstituted cyclopropylene, , or F-

substituted cyclopropylene, e.g., .

[0067] In some preferred embodiments, the compound of Formula I can be characterized as having a structure according to Formula I-3:



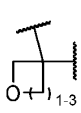
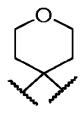
Formula I-3,

wherein the variables are defined herein.

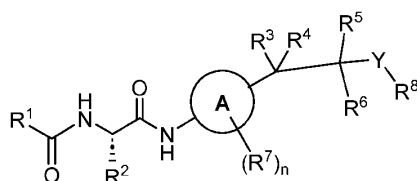
[0068] In some preferred embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, etc., R³ and R⁴, together with the carbon atom they are both attached to, are joined to a 4-8 membered heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O, N, and S, wherein the sulfur atom, if present, is optionally oxidized, and the 4-8 membered heterocyclic ring is optionally

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substituted, for example, R^3 and R^4 , together with the carbon atom they are both attached to,

are joined to form  or , which is optionally substituted.

[0069] In some preferred embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-3, etc., L^1 is null. For example, in some preferred embodiments, the compound of Formula I can have a structure according to Formula I-2:



Formula I-2,

wherein the variables are defined herein.

[0070] In some embodiments, L^1 can be an optionally substituted C_{1-4} alkylene. In some embodiments, L^1 can be an optionally substituted C_{1-4} heteroalkylene.

[0071] In Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^5 is typically hydrogen or C_{1-4} alkyl optionally substituted with F (e.g., methyl, or fluorine substituted methyl). In some preferred embodiments, R^5 is hydrogen.

[0072] In some embodiments, R^5 can also be an optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or optionally substituted 3-8 membered ring, such as an optionally substituted 3-5 membered carbocyclic or 4-5 membered heterocyclic ring.

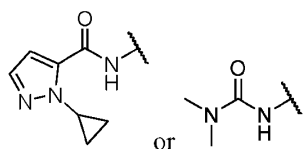
[0073] In some embodiments, when applicable, one of R^3 and R^4 , together with R^5 , and the intervening atoms, are joined to form an optionally substituted 3-8 membered carbocyclic or 4-8 membered heterocyclic ring, and the other of R^3 and R^4 are defined herein.

[0074] In Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^6 is typically $N(G^{2A})C(O)G^{2B}$, $N(G^{2A})C(O)OG^{2B}$, $N(G^{2A})C(O)NG^{2A}G^{2B}$, $N(G^{2A})SO_2G^{2B}$, or $N(G^{2A})SO_2NG^{2A}G^{2B}$, wherein G^{2A} and G^{2B} are defined herein, preferably, G^{2A} at each occurrence is independently hydrogen or an optionally substituted C_{1-6} alkyl; and

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G^{2B} is R^{X1} , $(C_{1-4} \text{ alkylene})-R^{X1}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X1}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, wherein R^{X1} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C_{3-8} carbocyclic ring, optionally substituted 5- or 6-membered heteroaryl ring, or optionally substituted 4-8 membered heterocyclic ring), wherein, when substituted, the optionally substituted group of G^{2A} or R^{X1} is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0075] In some embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^6 can be $N(G^{2A})C(O)G^{2B}$, wherein G^{2A} and G^{2B} are defined and preferred herein. For example, in some embodiments, R^6 can be $NHC(O)G^{2B}$, wherein G^{2B} is defined and preferred herein. For example, in some



embodiments, R^6 can be

or

[0076] In some embodiments, G^{2A} at each occurrence is independently hydrogen or a C_{1-4} alkyl optionally substituted with one or more G^{S2} , wherein G^{S2} at each occurrence is independently deuterium, F, or OH.

[0077] In some embodiments, G^{2B} is R^{X1} , wherein R^{X1} is defined and preferred herein.

[0078] In some embodiments, G^{2B} is $(C_{1-4} \text{ alkylene})-R^{X1}$, such as a $(C_{1-2} \text{ alkylene})-R^{X1}$, wherein R^{X1} is defined and preferred herein.

[0079] In some embodiments, G^{2B} is $(C_{1-4} \text{ heteroalkylene})-R^{X1}$, wherein R^{X1} is defined and preferred herein.

[0080] In some preferred embodiments, R^{X1} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-10 membered ring (e.g., carbocyclic, heterocyclic, or heteroaryl ring) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. For example, in some embodiments, R^{X1} is C_{1-4} alkyl optionally substituted with one or more G^{S1} . In some embodiments, R^{X1} is C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} . In some embodiments, R^{X1} is C_{3-7} carbocyclic optionally substituted with one or more G^{S3} . In some embodiments, R^{X1} is 4-7 membered heterocyclic optionally substituted with one or more G^{S3} .

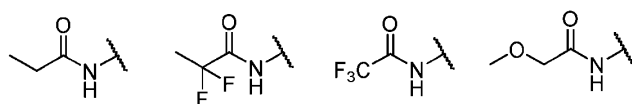
[0081] In some embodiments, G^{2B} is R^{X1} or $(C_{1-4} \text{ alkylene})-R^{X1}$, wherein R^{X1} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{3-7} carbocyclic optionally substituted with one or more G^{S3} , 5- or 6-membered heteroaryl ring optionally substituted with one or more G^{S3} ; or 4-7 membered heterocyclic optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0082] In some embodiments, G^{2B} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-10 membered ring (e.g., carbocyclic, heterocyclic, or heteroaryl ring) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some embodiments, G^{2B} is G^{2C} or G^{2D} as defined herein.

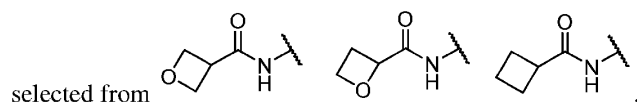
[0083] In some embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^6 can be $NHC(O)G^{2C}$, $NHC(O)OG^{2C}$, or $NHC(O)NHG^{2C}$, and G^{2C} is C_{1-4} alkyl (e.g., methyl or ethyl) optionally substituted with one or more G^{S1} , C_{3-6} cycloalkyl (e.g., cyclobutyl) optionally substituted with one or more G^{S3} , 4-7 membered heterocyclic ring (e.g., oxetanyl) optionally substituted with

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one or more G^{S3} , or a 5 or 6 membered heteroaryl optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. In some preferred embodiments, R^6 is $NHC(O)G^{2C}$, wherein G^{2C} is defined herein. In some embodiments, R^6 is selected from



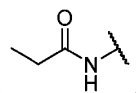
. In some embodiments, R^6 is



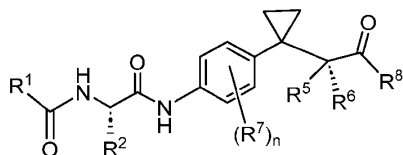
selected from

[0084] In some embodiments, in Formula I or any of the applicable subformulae herein, such as Formula I-A, I-A1, I-A2, I-A3, I-1, I-2, I-3, I-4, etc., R^6 can be $NHC(O)G^{2D}$, wherein G^{2D} is (1) C_{1-4} alkyl optionally substituted with one or more deuterium and/or F, or (2) C_{3-6} cycloalkyl optionally substituted with methyl and/or F. For example, in some specific embodiments, G^{2D} is C_{1-4} alkyl optionally substituted with one or more deuterium and/or F,

such as ethyl. In some preferred embodiments, R^6 is



[0085] In Formula I or any of the applicable subformulae herein, Y is typically C(O). For example, in some preferred embodiments, the compound of Formula I can have a structure according to Formula I-4:

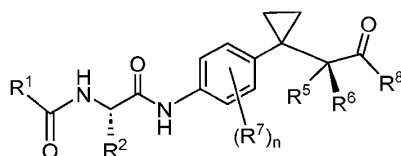


Formula I-4,

wherein the variables are defined herein.

[0086] In some embodiments, the compound of Formula I can have a structure according to Formula I-4-D2:

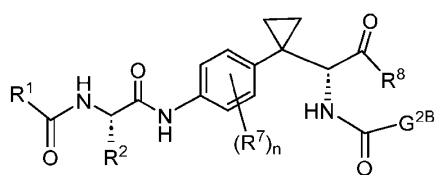
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Formula I-4-D2,

wherein the variables are defined herein.

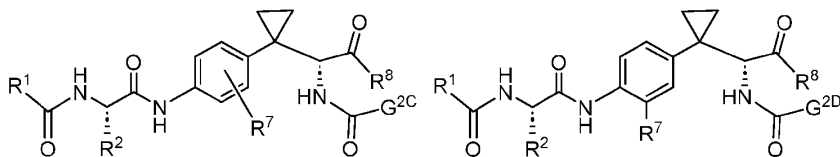
[0087] For example, in some embodiments, the compound of Formula I-4 can have a structure according to Formula I-4a:



Formula I-4a,

wherein the variables are defined herein.

[0088] In some more specific embodiments, the compound of Formula I-4a can have a structure according to Formula I-4a-1 or 1-4a-2:

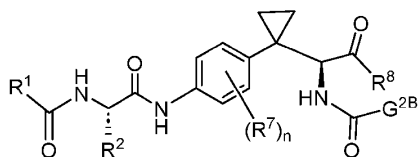


Formula I-4a-1

Formula I-4a-2,

wherein the variables are defined herein.

[0089] In some embodiments, the compound of Formula I-4-D2 can have a structure according to Formula I-4a-D2:

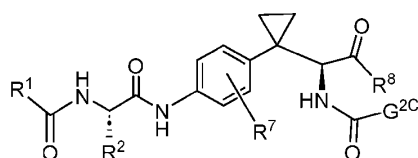


Formula I-4a-D2,

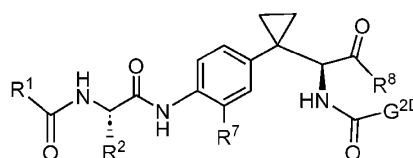
wherein the variables are defined herein.

[0090] In some more specific embodiments, the compound of Formula I-4a-D2 can have a structure according to Formula I-4a-1-D2 or 1-4a-2-D2:

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Formula I-4a-1-D2



Formula I-4a-2-D2,

wherein the variables are defined herein.

[0091] In some embodiments, Y can be a SO₂ group.

[0092] In some embodiments, Ring A in Formula I can be unsubstituted phenylene or unsubstituted 6-membered heteroarylene (e.g., pyridylene, pyridazinylene, pyrimidinylene, etc.), i.e., n is 0.

[0093] In some embodiments, Ring A in Formula I can be a phenylene or 6-membered heteroarylene (e.g., pyridylene, pyridazinylene, pyrimidinylene, etc.), which is substituted with 1-4 instances of R⁷ as valency permits, i.e., n is 1-4. Typically, when substituted, the phenylene or 6-membered heteroarylene is substituted with 1 or 2 R⁷ as defined herein.

[0094] A variety of groups can be a suitable R⁷ for an applicable Formula I or a subformula herein, which includes deuterium, halogens, cyano, alkyls, alkenyls, alkynyls, heteroalkyls, ring structures such as carbocyclic or heterocyclic rings, alcohols, amines, alkoxy groups, esters, amides, sulfones, sulfonamides, etc.

[0095] In some embodiments, two R⁷ can be joined to form an optionally substituted 4-8 membered ring, such as a 4-8 membered carbocyclic or heterocyclic ring or a phenyl ring, or 5 or 6 membered heteroaryl ring. In some embodiments, one instance of R⁷ and either R³ or R⁴, together with the intervening atoms, are joined to form an optionally substituted 5-8 membered carbocyclic or heterocyclic ring. In such embodiments, any remaining R⁷ can be independently selected from deuterium, halogen, CN, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, optionally substituted 3-8 membered ring, or J⁴-J⁵-J⁶-G⁴, as defined herein.

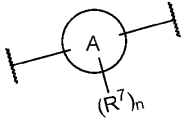
[0096] In some embodiments, when present, one or more instances of R⁷ can be represented by the general formula J⁴-J⁵-J⁶-G⁴ as defined herein. The combination of J⁴, J⁵, and J⁶ is not particularly limited, which can preferably be (a) a linker of O, NG⁴, C(O), S, SO, SO₂, or P(O)G⁴, when two of J⁴, J⁵, and J⁶ are null, or (b) a linker of amide (C(O)NG⁴), ester (C(O)O), sulfonamide (SO₂NG⁴), etc., when one of J⁴, J⁵, and J⁶ is null, or (c) a linker of

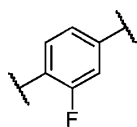
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carbamate (OC(O)NG^4), urea ($\text{NG}^4\text{C(O)NG}^4$), sulfamoylamino ($\text{NG}^4\text{SO}_2\text{NG}^4$), etc., when none of J^4 , J^5 , and J^6 is null.

[0097] In some embodiments, R^7 at each occurrence is independently deuterium, halogen (e.g., F, Cl, or Br), CN, C_{1-6} alkyl optionally substituted with deuterium and/or F, C_{2-6} alkenyl optionally substituted with deuterium and/or F, C_{2-6} alkynyl optionally substituted with deuterium and/or F, C_{1-6} heteroalkyl optionally substituted with deuterium and/or F, optionally substituted 3-7 membered carbocyclic or heterocyclic ring having 1 or 2 ring heteroatoms, OG^4 , NG^4G^4 , SG^4 , C(O)G^4 , or $\text{C(O)NG}^4\text{G}^4$, wherein G^4 at each occurrence is independently hydrogen, C_{1-6} alkyl optionally substituted with deuterium and/or F, or optionally substituted 3-7 membered carbocyclic or heterocyclic ring having 1 or 2 ring heteroatoms, wherein each of the optionally substituted 3-7 membered carbocyclic or heterocyclic ring is optionally substituted with one or more substituents independently selected from deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0098] In some more specific embodiments, R^7 at each occurrence is independently F, Cl, C_{1-4} alkyl optionally substituted with F, C_{2-4} alkenyl optionally substituted with F, C_{2-4} alkynyl optionally substituted with F, or C_{1-4} heteroalkyl optionally substituted with F. In some

specific embodiments, the moiety of  in Formula I or a subformula can be



, wherein the F is ortho to the amide NH in Formula I.

[0099] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) is NG^3G^3 , wherein G^3 is defined herein.

[0100] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) is $\text{NG}^{3A}\text{G}^{3B}$, wherein:

wherein G^{3A} is hydrogen or an optionally substituted C_{1-6} alkyl; and

G^{3B} is $\text{R}^{\text{X}2}$, $(\text{C}_{1-4} \text{ alkylene})\text{-R}^{\text{X}2}$, or $(\text{C}_{1-4} \text{ heteroalkylene})\text{-R}^{\text{X}2}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized,

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wherein R^{X2} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C_{3-8} carbocyclic ring, or optionally substituted 4-8 membered heterocyclic ring),

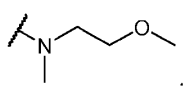
wherein, when substituted, the optionally substituted group of G^{3A} or R^{X2} is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0101] In some embodiments, G^{3B} is R^{X2} , wherein R^{X2} is defined and preferred herein.

[0102] In some embodiments, G^{3B} is $(C_{1-4} \text{ alkylene})-R^{X2}$, such as a $(C_{1-2} \text{ alkylene})-R^{X2}$, wherein R^{X2} is defined and preferred herein.

[0103] In some embodiments, G^{3B} is $(C_{1-4} \text{ heteroalkylene})-R^{X2}$, wherein R^{X2} is defined and preferred herein.

[0104] In some preferred embodiments, R^{X2} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-10 membered ring (e.g., carbocyclic, heterocyclic, or heteroaryl ring) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. For example, in some embodiments, R^{X2} is C_{1-4} alkyl optionally substituted with one or more G^{S1} . In some embodiments, R^{X2} is C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} . In some embodiments, R^{X2} is C_{3-7} carbocyclic optionally substituted with one or more G^{S3} . In some embodiments, R^{X2} is 4-7 membered heterocyclic optionally substituted with one or more G^{S3} . For example, in some

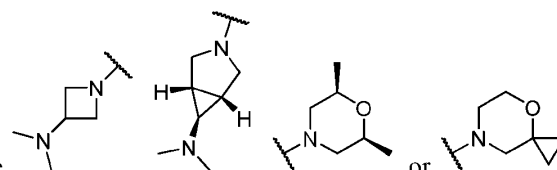
embodiments, R^8 can be .

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[0105] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) is an optionally substituted 4-8 membered heterocyclic ring having 1-3 ring heteroatoms, with one of the ring heteroatoms being a ring nitrogen, which is bonded to Y, and any remaining ring heteroatom(s) being independently selected from N, O, and S, wherein the sulfur atom, if present, is optionally oxidized.

[0106] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) can

have a structure represented by M-1,  (M-1), which is an optionally substituted ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, and azaspiro[3,3]heptane, wherein, when substituted, the optionally substituted ring is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, R^{X3} , OR^{X3} , $C(O)R^{X3}$, SO_2R^{X3} , $(C_{1-4} \text{ alkylene})-R^{X3}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X3}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, or two substituents together with the atoms they are bonded to are joined to form a 3-6 membered ring, which can be a spiro, fused, or bridged ring, wherein R^{X3} at each occurrence is independently C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. For example, in some

embodiments, R^8 can be  , or

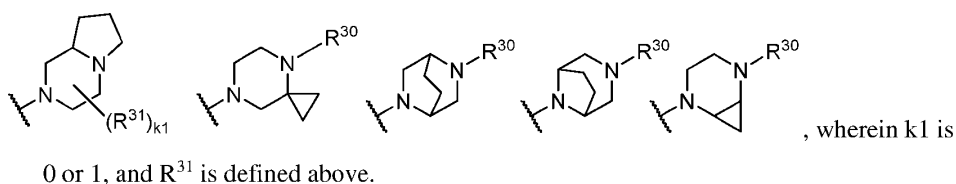
[0107] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) can

have a structure represented by M-2,  (M-2),

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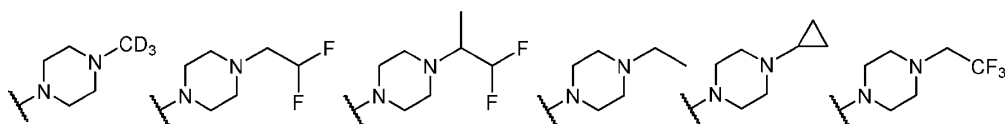
wherein R^{30} is hydrogen, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} , or $(C_{1-2}$ alkylene)-(3-6 membered ring), wherein the 3-6 membered ring (e.g., cyclopropyl) is optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, k is 0, 1, or 2, and

R^{31} at each occurrence is independently deuterium, oxo, or C_{1-4} alkyl optionally substituted with F, or two R^{31} , together with the intervening atom(s) are joined to form a ring, e.g., a fused or spiro cyclopropyl, or a bridged ring, or one R^{31} and R^{30} , together with the intervening atom(s) are joined to form a ring. For example, in some embodiments, R^8 can have a structure selected from:

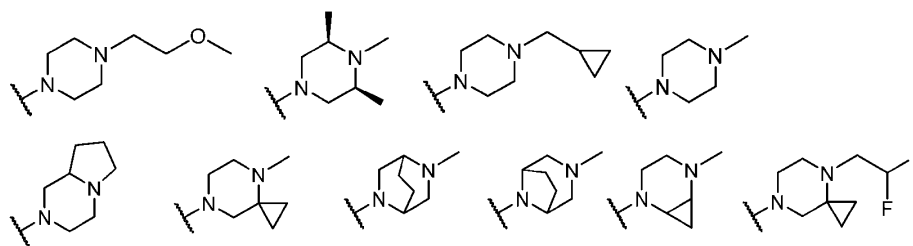


[0108] In some embodiments, in M-2, R^{30} is hydrogen.

[0109] In some embodiments, in M-2, R^{30} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , or R^{30} is cyclopropyl or $(C_{1-2}$ alkylene)-(cyclopropyl), wherein the cyclopropyl is optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F. For example, in some embodiments, R^{30} is C_{1-4} alkyl unsubstituted or substituted with F, such as methyl. In some specific embodiments, R^{30} is CH_3 , CD_3 , ethyl optionally substituted with 1-3 F (e.g., CH_2CF_2H , CH_2CF_3 , etc.), methoxyethyl, cyclopropylmethyl, cyclopropyl, etc. For example, in some embodiments, R^8 can have a structure selected from:



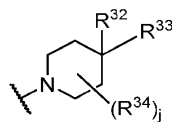
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[0110] In some embodiments, in M-2, k is 0.

[0111] In some embodiments, in M-2, k is 1 or 2, and R^{31} at each occurrence is C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, for example, R^{31} at each occurrence is methyl.

[0112] In some embodiments, R^8 in Formula I (e.g., any of the applicable subformulae) can



have a structure represented by M-3,

wherein

R^{32} is hydrogen, halogen, CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} ,

R^{33} is hydrogen, halogen, CN, OH, NH_2 , C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl (e.g., C_{1-4} alkoxy, C_{1-4} monoalkyl amine, or C_{2-4} dialkyl amine) optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} ,

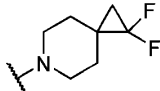
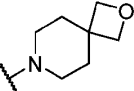
or R^{32} and R^{33} , together with the carbon they are both attached to, are joined to form $C(=O)$ or an optionally substituted 3-6 membered ring (e.g., cyclopropyl, cyclobutyl, oxetane, etc.),

wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F,

j is 0, 1, or 2, and

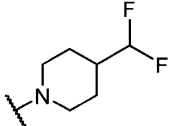
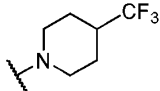
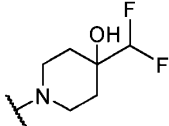
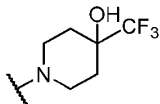
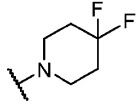
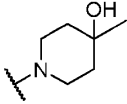
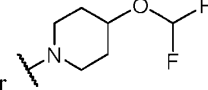
- 42 -

R^{34} at each occurrence is independently oxo, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with F, or two R^{34} , or one R^{34} and one of R^{32} and R^{33} , together with the intervening atom(s) are joined to form a ring, e.g., a spiro cyclopropyl, or a fused or bridged

ring, e.g., R^8 is , , etc.

[0113] In some embodiments, in M-3, R^{32} is hydrogen, F, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} alkoxy optionally substituted one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, e.g., R^{32} is F, CH_3 , CHF_2 , CF_3 , difluoromethoxy, etc.

[0114] In some embodiments, in M-3, R^{33} is hydrogen, OH, halogen (e.g., F), CN, or C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, e.g., R^{33} is hydrogen, F, CH_3 , OH, etc. For example, in some embodiments, R^8 can have a

structure of , , , , , , or .

[0115] In some embodiments, in M-3, j is 0.

[0116] In some embodiments, in M-3, j is 1 or 2, and R^{34} at each occurrence is independently OH, halogen, CN, or C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0117] In some embodiments, in Formula I, R^8 is an optionally substituted 4-14 membered heterocyclic ring, or an optionally substituted heteroaryl ring.

[0118] In some embodiments, in Formula I, R^8 is an optionally substituted 4-7 membered heterocyclic ring having 1 or 2 ring heteroatoms each independently N, O, or S, wherein the sulfur atom, if present, is optionally oxidized, wherein when substituted, the 4-7 membered heterocyclic ring is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable),

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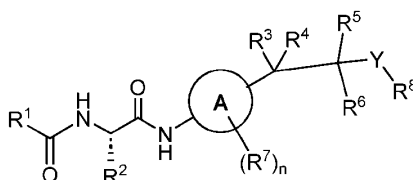
CN, R^{X4} , OR^{X4} , $C(O)R^{X4}$, SO_2R^{X4} , $(C_{1-4} \text{ alkylene})-R^{X4}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X4}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom is optionally oxidized,

wherein R^{X4} at each occurrence is independently C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

[0119] Exemplary definitions of each of the variables herein also include any of those shown in the specific compounds in Table 1 herein for the respective variable and those shown in enumerated exemplary Embodiments 1-28 herein.

[0120] In some embodiments, the present disclosure also provides a compound according to any of the enumerated exemplary Embodiments 1-28:

Embodiment 1. A compound of Formula I-2, or a pharmaceutically acceptable salt thereof:



Formula I-2

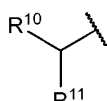
wherein:

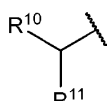
R^1 is a 5-membered heteroaryl selected from pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, furan, thiophene, imidazole, oxadiazole, thiadiazole, triazole, or tetrazole, which is unsubstituted or substituted with 1 or 2 independently selected R^{A1} , wherein R^{A1} is (i) C_{1-4} alkyl optionally substituted with deuterium and/or F, (ii) $(C_{1-2} \text{ alkylene})-C_{3-4}$ cycloalkyl, such as cyclopropylmethyl, wherein the C_{1-2} alkylene and C_{3-4} cycloalkyl are each independently optionally substituted with methyl, deuterium, and/or F; or (iii) C_{3-4} cycloalkyl optionally substituted with methyl and/or F;

R^2 is selected from:

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- i) a monocyclic C₃₋₈ cycloalkyl optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1};
- ii) a polycyclic C₄₋₁₀ carbocyclyl optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}; or



- iii) a structure of , wherein (1) R¹⁰ is C₁₋₄ alkyl optionally substituted with one or more G^{S1}, and R¹¹ is a C₃₋₆ cycloalkyl or phenyl; (2) R¹⁰ is a C₃₋₆ cycloalkyl and R¹¹ is a phenyl; (3) R¹⁰ and R¹¹ are independently a C₃₋₆ cycloalkyl; or (4) R¹⁰ and R¹¹ are independently a phenyl; wherein the C₃₋₆ cycloalkyl or phenyl in each of (1)-(4) is independently optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}; or
- iv) a 10-14 membered polycyclic heterocyclyl having 1-3 ring heteroatoms independently selected from S, O, and N, wherein the 10-14 membered polycyclic heterocyclyl has a fused ring structure from a 5-7 membered heterocyclic ring and a phenyl or 6-membered heteroaryl ring, optionally one additional ring which forms a spiro, fused, or bridged structure with the 5-7 membered heterocyclic ring, and wherein the 10-14 membered polycyclic heterocyclyl is optionally substituted with one or more substituents each independently halogen, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F;

Ring A is phenylene or 6-membered heteroarylene (e.g., pyridylene, pyridazinylene, pyrimidinylene, etc.), which is optionally substituted with 1 or 2 instances of R⁷ as valency permits;

Y is C(O);

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R³ and R⁴ are each independently C₁₋₄ alkyl optionally substituted with one or more G^{S2}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S2}, or

R³ and R⁴, together with the carbon atom they are both attached to, are joined to form an optionally substituted 3-7 membered carbocyclic ring, or an optionally substituted 4-8 membered heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O, N, and S, wherein the sulfur atom, if present, is optionally oxidized;

R⁵ is hydrogen;

R⁶ is N(G^{2A})C(O)G^{2B};

R⁷ at each occurrence is independently F, Cl, C₁₋₄ alkyl optionally substituted with F, C₂₋₄ alkenyl optionally substituted with F, C₂₋₄ alkynyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F;

R⁸ is NG³G³ or an optionally substituted 4-8 membered heterocyclic ring, wherein G³ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring; or two G³, together with the nitrogen atom they are both attached to, are joined to form an optionally substituted 4-8 membered heterocyclic ring; and

"n" is 0, 1, or 2,

wherein:

G^{2A} at each occurrence is independently hydrogen or a C₁₋₄ alkyl optionally substituted with one or more G^{S2},

G^{2B} is R^{X1}, (C₁₋₄ alkylene)-R^{X1}, or (C₁₋₄ heteroalkylene)-R^{X1}, wherein the C₁₋₄ heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, wherein

R^{X1} is C₁₋₄ alkyl optionally substituted with one or more G^{S1}, C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, C₃₋₇ carbocyclic optionally substituted with one or more G^{S3}, 5- or 6-membered heteroaryl ring optionally substituted with one or more G^{S3}; or 4-7 membered heterocyclic optionally substituted with one or more G^{S3};

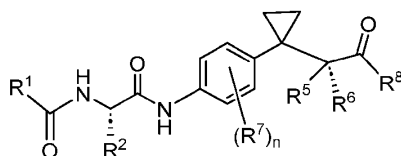
G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F;

G^{S2} at each occurrence is independently deuterium, F, or OH; and

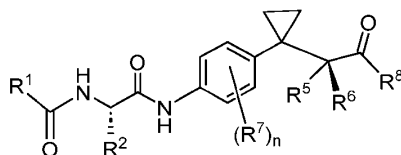
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G^{S3} at each occurrence is independently deuterium, F, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F.

Embodiment 2. The compound of Embodiment 1, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-4 or I-4-D2:



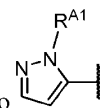
Formula I-4,



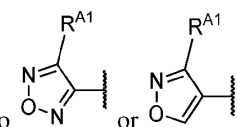
Formula I-4-D2,

wherein R¹, R², R⁵, R⁶, R⁷, R⁸, and n are as defined in Embodiment 1.

Embodiment 3. The compound of Embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R¹ has a structure according to



Embodiment 4. The compound of Embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R¹ has a structure according to



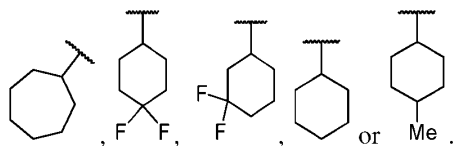
Embodiment 5. The compound of any of Embodiments 1-4, or a pharmaceutically acceptable salt thereof, R^{A1} at each occurrence is independently (i) C₁₋₄ alkyl optionally substituted with deuterium and/or F, e.g., methyl, CD₃, ethyl, isopropyl, difluoromethyl, 2,2-difluoroethyl; (ii) cyclopropylmethyl; or (iii) C₃₋₄ cycloalkyl optionally substituted with F, such as cyclopropyl.

Embodiment 6. The compound of any of Embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein R² is a monocyclic C₃₋₇ cycloalkyl, optionally

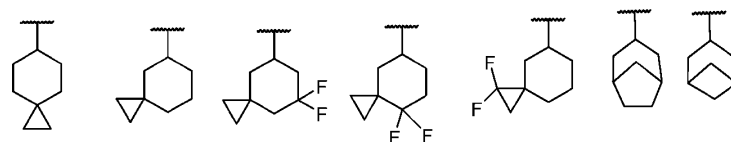
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substituted with one or more substituents each independently deuterium, F, or C₁₋₃ alkyl optionally substituted with one or more G^{S2}.

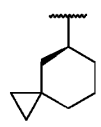
Embodiment 7. The compound of any of Embodiments 1-5, or a pharmaceutically

acceptable salt thereof, wherein R² is .

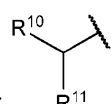
Embodiment 8. The compound of any of Embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein R² is selected from:



Embodiment 9. The compound of any of Embodiments 1-5, or a pharmaceutically

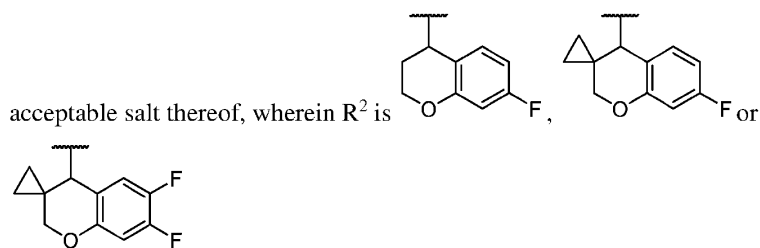
acceptable salt thereof, wherein R² is .

Embodiment 10. The compound of any of Embodiments 1-5, or a pharmaceutically

acceptable salt thereof, wherein R² has a structure of , and R¹⁰ and R¹¹ are independently selected from cyclopropyl, methylcyclopropyl, cyclobutyl, phenyl, and phenyl substituted with one or two halogens independently selected from F and Cl.

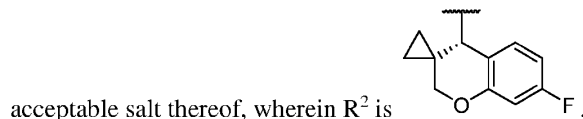
Embodiment 11. The compound of Embodiment 10, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ and R¹¹ are the same.

Embodiment 12. The compound of any of Embodiments 1-5, or a pharmaceutically

acceptable salt thereof, wherein R² is .

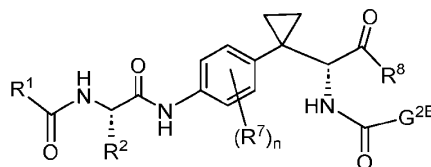
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Embodiment 13. The compound of any of Embodiments 1-5, or a pharmaceutically

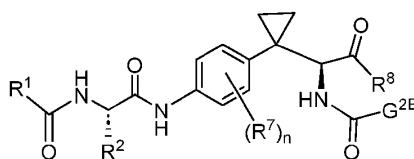


Embodiment 14. The compound of any of Embodiments 1-13, or a pharmaceutically acceptable salt thereof, wherein R^6 is NHC(O)G^{2B} , wherein G^{2B} is defined in Embodiment 1.

Embodiment 15. The compound of any of Embodiments 1-14, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-4a or I-4a-D2,



Formula I-4a

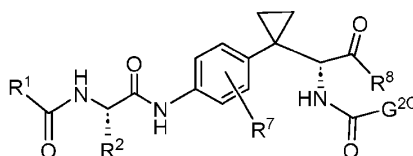


Formula I-4a-D2.

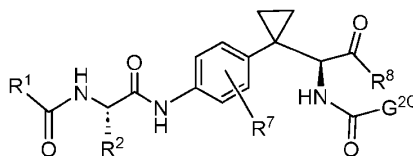
Embodiment 16. The compound of any of Embodiments 1-15, or a pharmaceutically acceptable salt thereof, wherein R^6 is NHC(O)G^{2C} , or G^{2B} is G^{2C} , and G^{2C} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{3-6} cycloalkyl optionally substituted with one or more G^{S3} , 4-7 membered heterocyclic ring optionally substituted with one or more G^{S3} , or a 5 or 6 membered heteroaryl optionally substituted with one or more G^{S3} , wherein G^{S1} and G^{S3} are as defined in Embodiment 1.

Embodiment 17. The compound of any of Embodiments 1-16, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-4a-1 or I-4a-1-D2:

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Formula I-4a-1,

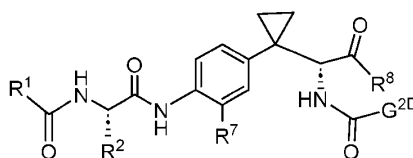


Formula I-4a-1-D2.

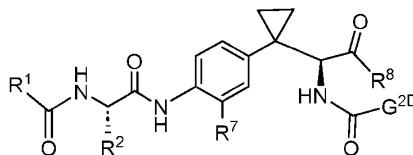
Embodiment 18. The compound of any of Embodiments 1-17, or a pharmaceutically acceptable salt thereof, wherein R^6 is NHC(O)G^{2D} , or G^{2B} is G^{2D} , and G^{2D} is C_{1-4} alkyl optionally substituted with one or more deuterium and/or F.

Embodiment 19. The compound of any of Embodiments 1-17, or a pharmaceutically acceptable salt thereof, wherein R^6 is NHC(O)G^{2D} , or G^{2B} is G^{2D} , and G^{2D} is a C_{3-6} cycloalkyl optionally substituted with methyl and/or F.

Embodiment 20. The compound of any of Embodiments 1-19, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-4a-2 or I-4a-2-D2:



Formula I-4a-2



Formula I-4a-2-D2.

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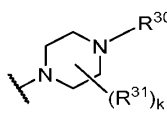
Embodiment 21. The compound of any of Embodiments 1-20, or a pharmaceutically acceptable salt thereof, wherein as applicable, n is 0 or 1.

Embodiment 22. The compound of any of Embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein R^7 at each occurrence is independently F, Cl, C_{1-4} alkyl optionally substituted with F, or C_{1-4} alkoxy optionally substituted with F, for example, R^7 at each occurrence is F.

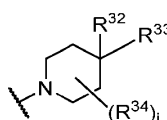
Embodiment 23. The compound of any of Embodiments 1-22, or a pharmaceutically

acceptable salt thereof, wherein R^8 has a structure according to M-1,  (M-1), which is an optionally substituted ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1,1,dioxide, and azaspiro[3,3]heptane, wherein the optionally substituted ring is optionally substituted with one or more substituents as described herein, e.g., as described in original filed claim 49.

Embodiment 24. The compound of any of Embodiments 1-22, or a pharmaceutically

acceptable salt thereof, wherein R^8 has a structure according to M-2,  (M-2), wherein R^{30} , R^{31} , and k are defined herein, e.g., as defined in any of the original filed claims 50-53.

Embodiment 25. The compound of any of Embodiments 1-22, or a pharmaceutically

acceptable salt thereof, wherein R^8 has a structure according to M-3,  (M-3), wherein R^{32} , R^{33} , R^{34} , and j are defined herein, e.g., as defined in any of the original filed claims 54-58.

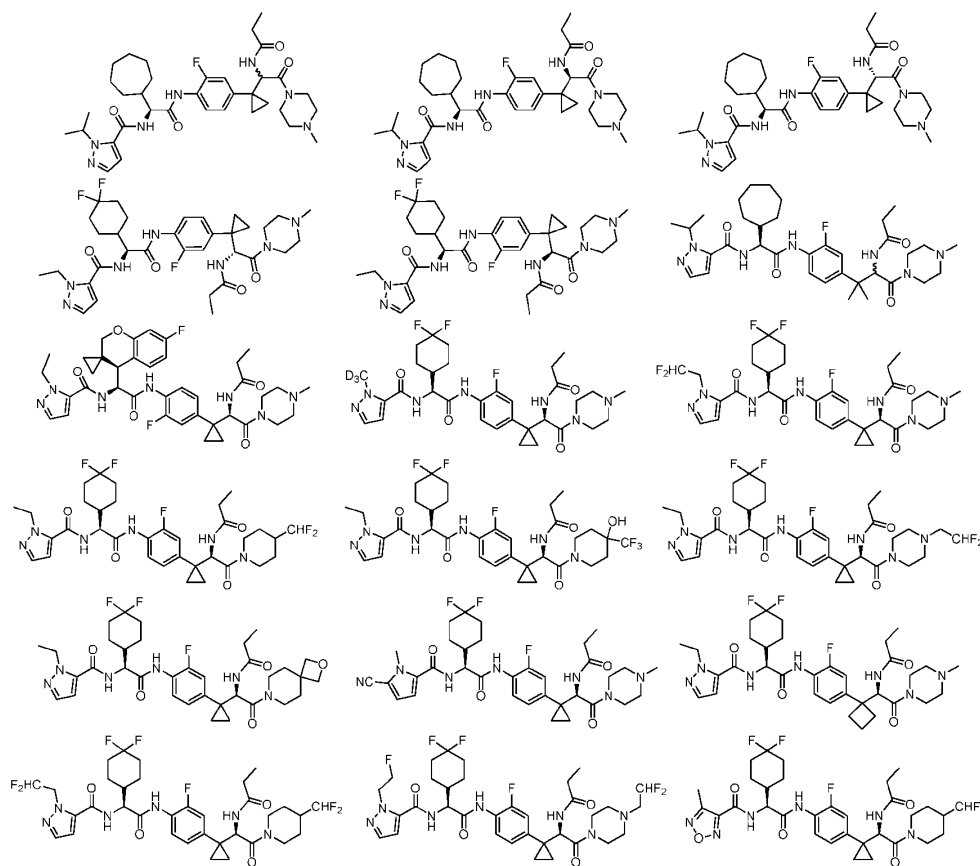
Embodiment 26. The compound of any of Embodiments 1-25, or a pharmaceutically acceptable salt thereof, wherein G^{S1} at each occurrence is F; and G^{S2} at each occurrence is F.

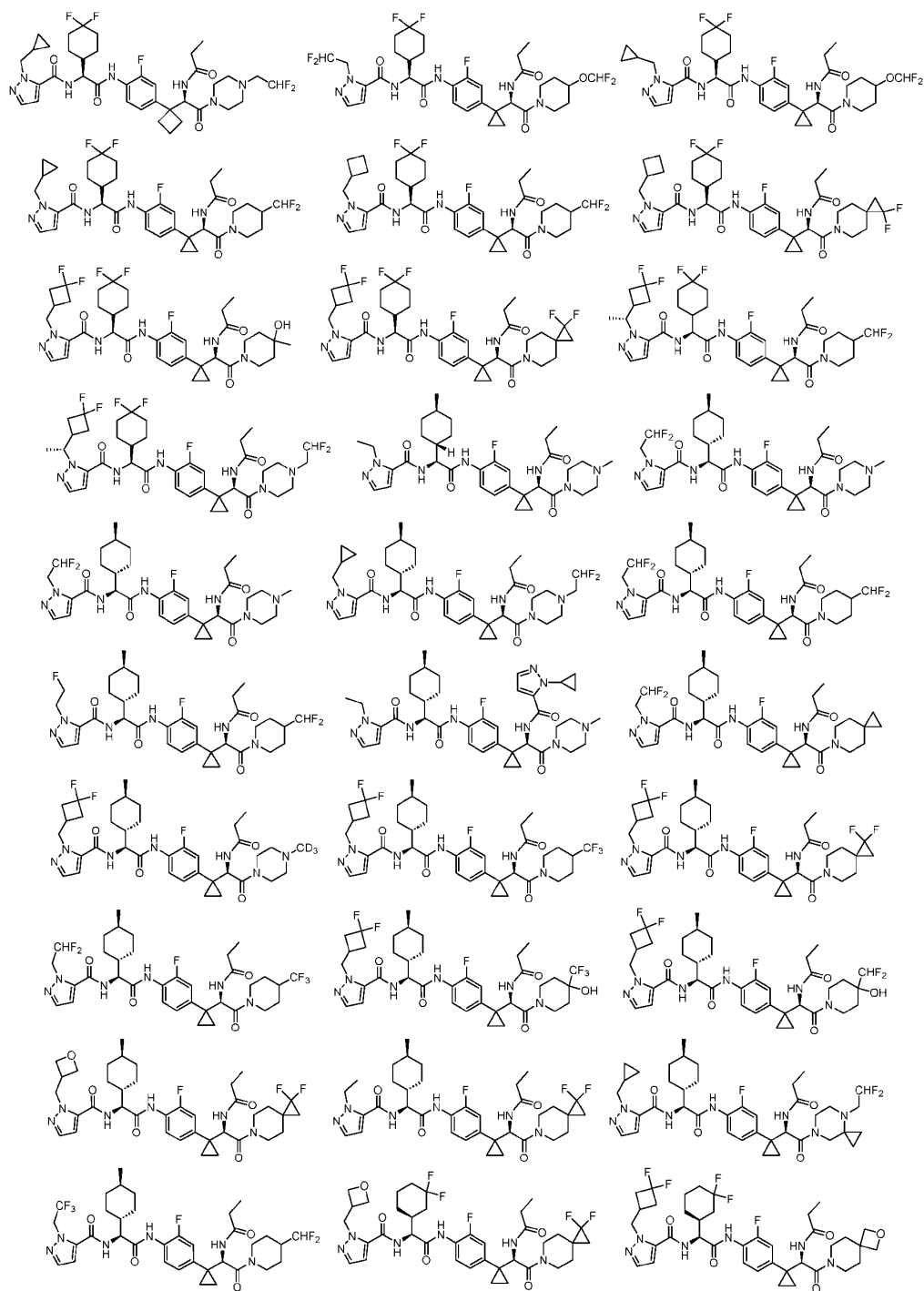
Embodiment 27. The compound of any of Embodiments 1-26, or a pharmaceutically acceptable salt thereof, wherein each variable in Formula I-2 can be independently selected from any of the respective specific groups shown in compounds of Table 1.

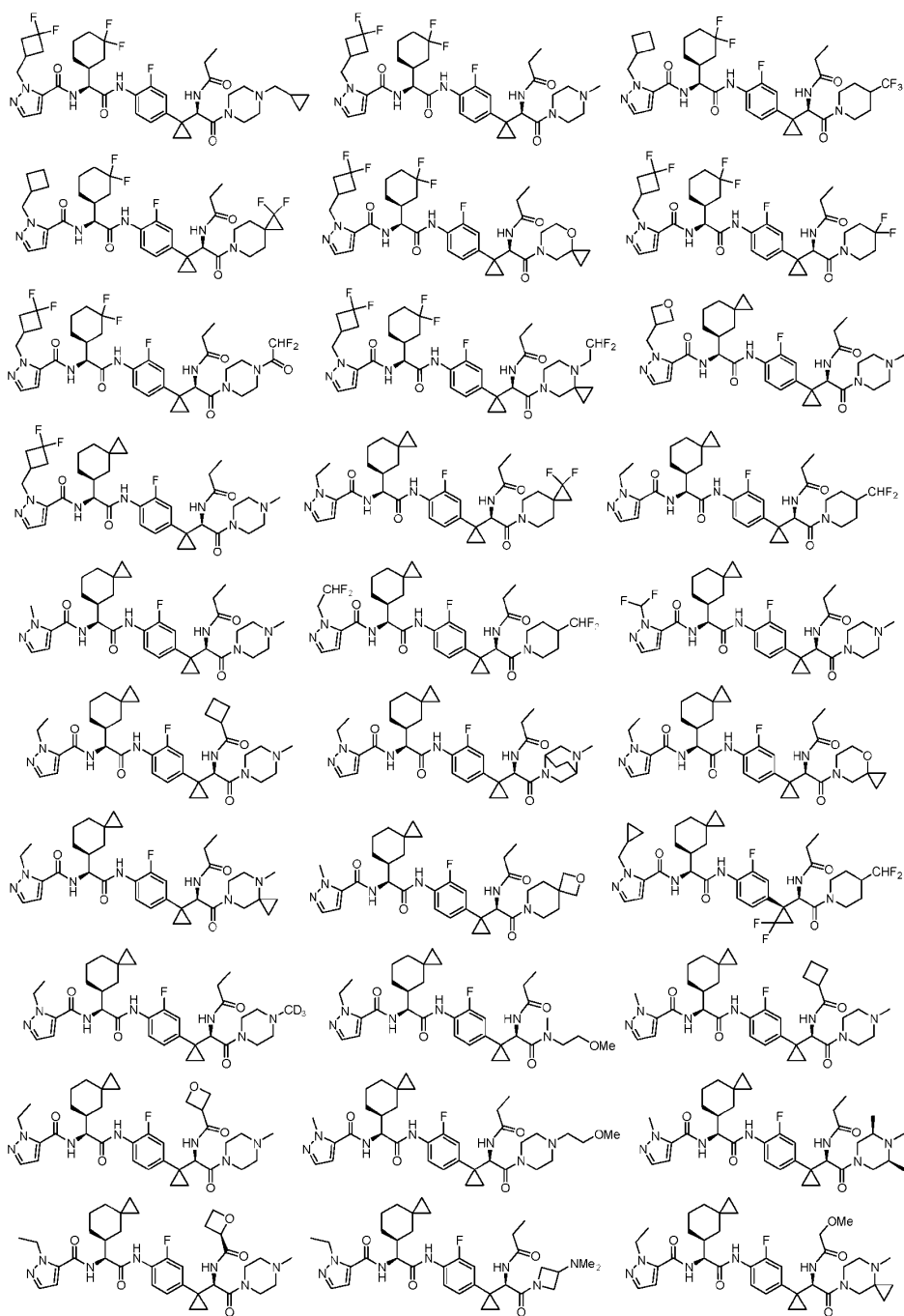
Embodiment 28. The compound of any of Embodiments 1-26, or a pharmaceutically acceptable salt thereof, wherein as applicable, each variable in Formula I-2 can have its respective definition that is defined herein and within the definition of Embodiment 1.

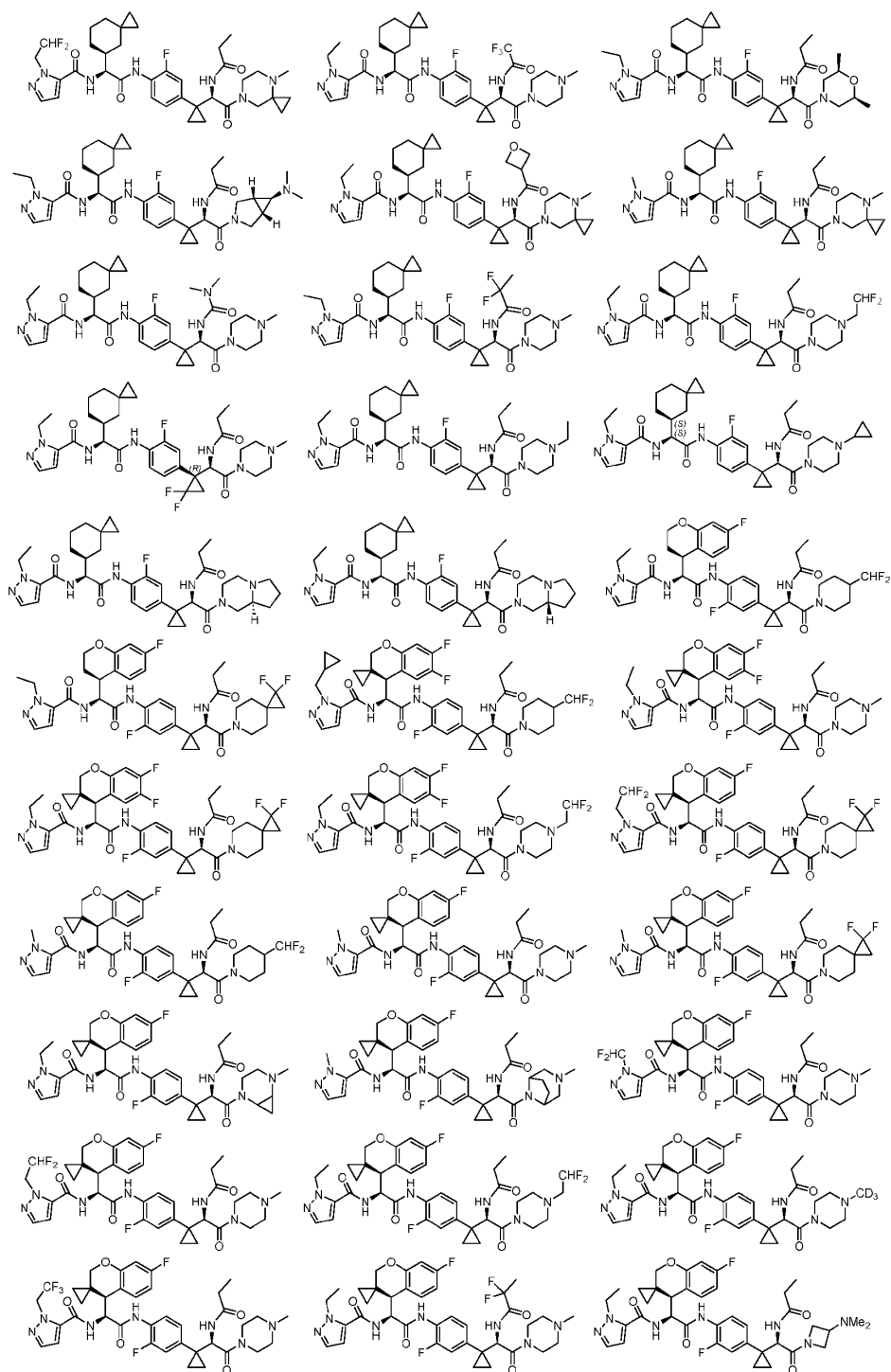
[0121] In some embodiments, the present disclosure also provides a compound selected from Table 1 below, a deuterated analog thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

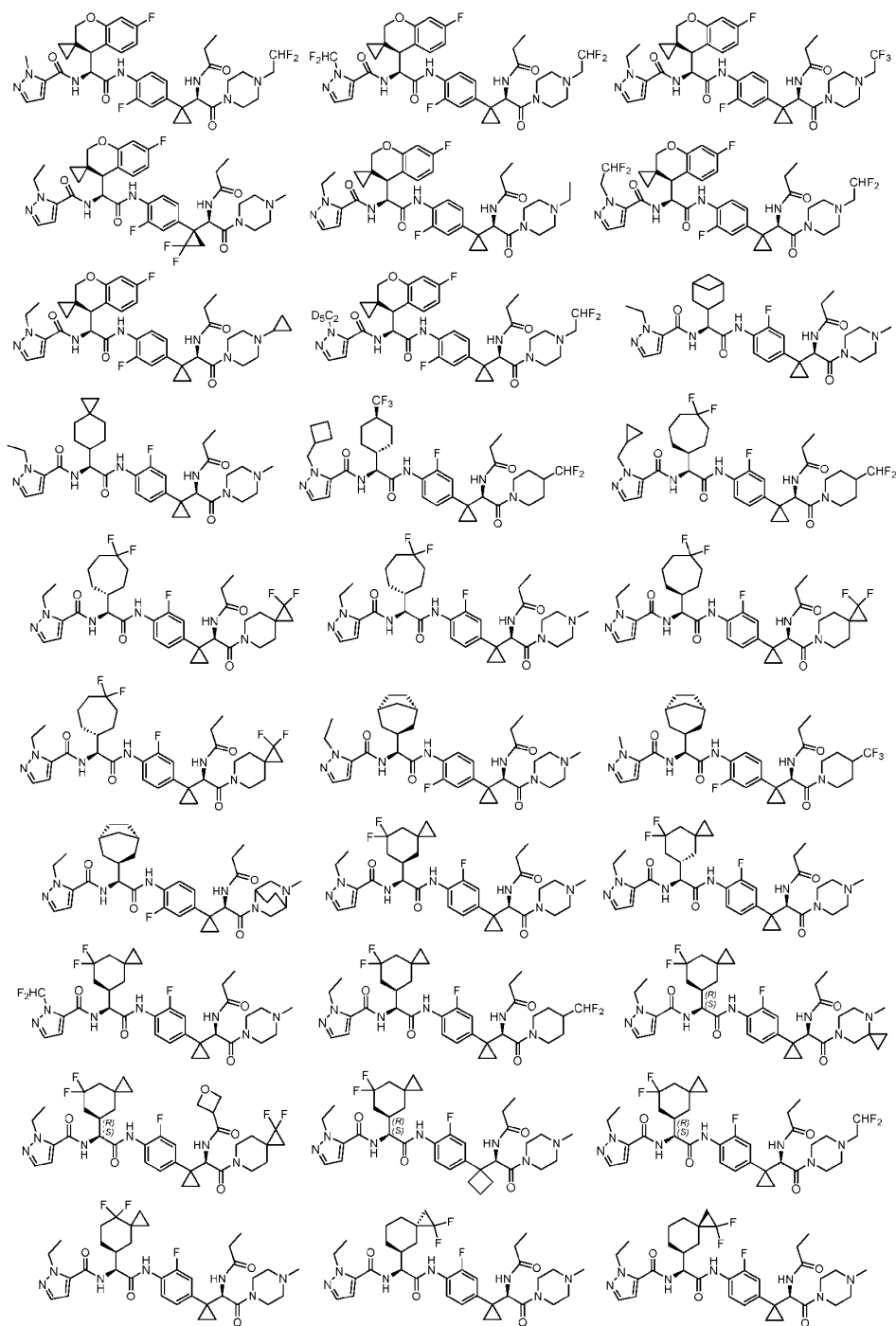
Table 1. List of Compounds



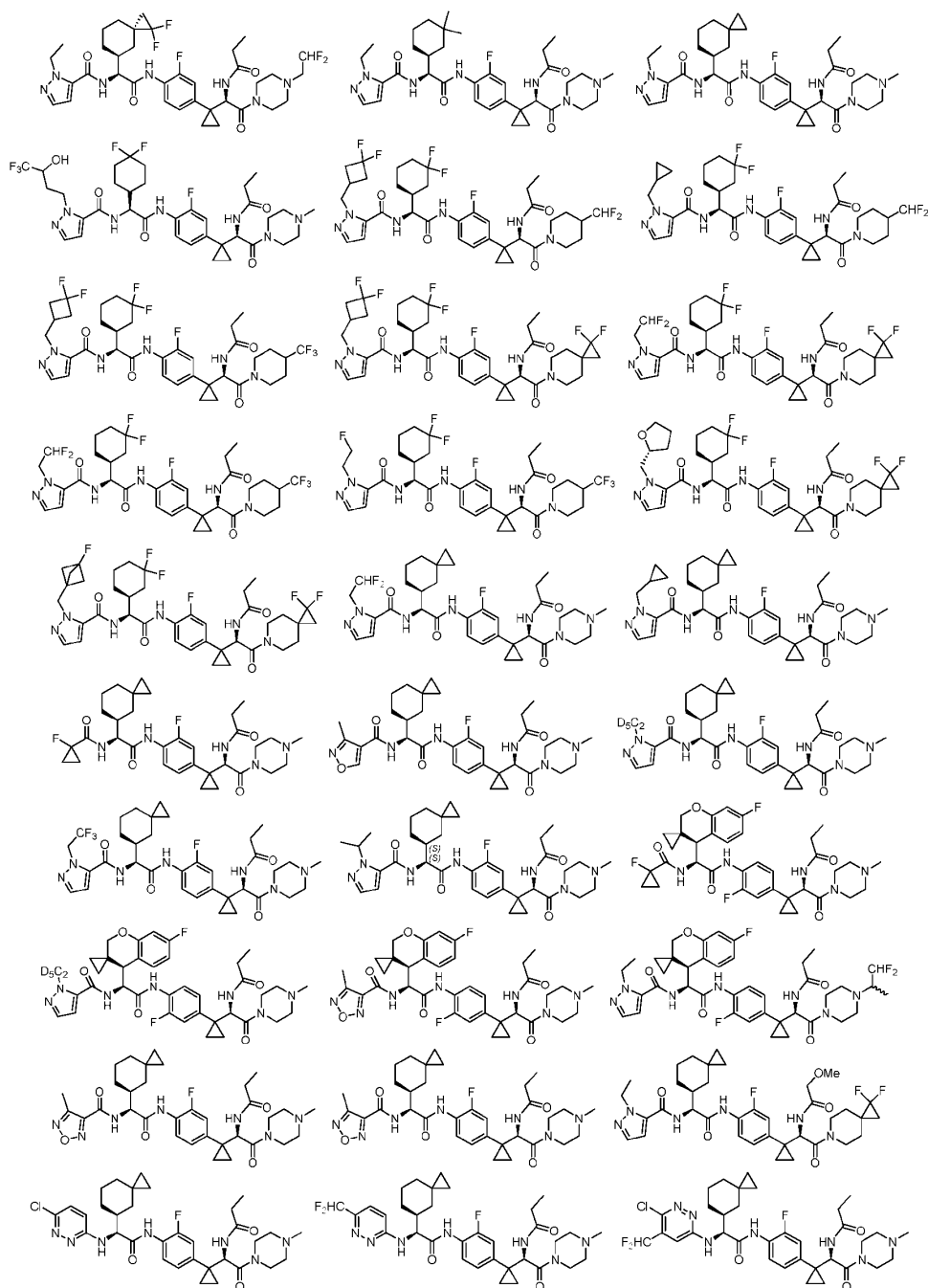


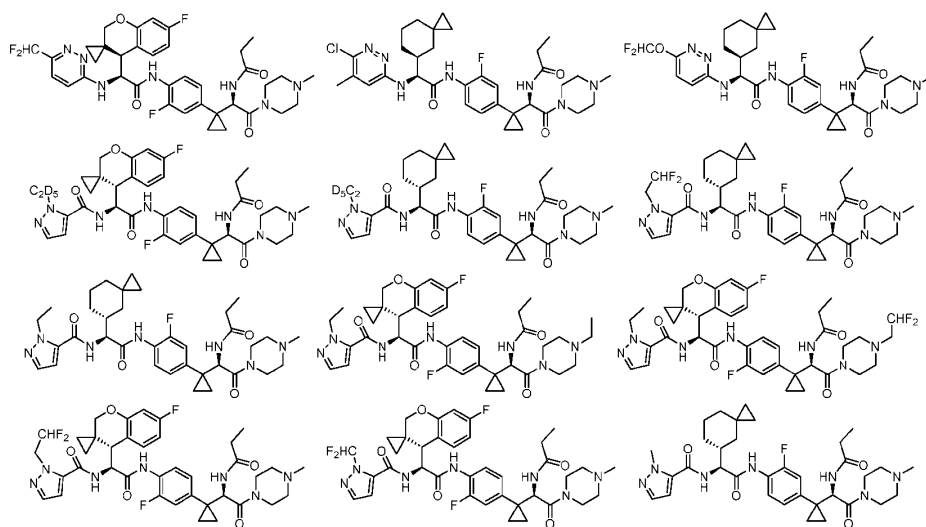






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It should be understood that the wiggly bond in the structure(s) indicates that the chiral center to which the wiggly bond is attached can be in either an R configuration or an S configuration, both stereoisomers and any mixtures thereof are contemplated in the present disclosure. Stereoisomers of any of the foregoing listed compounds, especially those with R² group being in a different stereochemistry, are also specifically contemplated in this disclosure.

[0122] In some embodiments, to the extent applicable, the genus of compounds described herein also excludes any specifically known single compounds prior to this disclosure. In some embodiments, to the extent applicable, any sub-genus or species of compounds prior to this disclosure that are entirely within a genus of compounds described herein can also be excluded from such genus herein.

[0123] The compounds of the present disclosure can be readily synthesized by those skilled in the art in view of the present disclosure. Exemplified syntheses are also shown in the Examples section. Certain synthetic starting materials or intermediates useful for the preparation of compounds of the present disclosure may be prepared according to published procedures, such as those described in US 2020/0247785, WO 2020/146194, WO 2021/055376, WO 2023/283453, WO 2022/007461, etc.

[0124] As will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting

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and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in "Protective Groups in Organic Synthesis", 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, and references cited therein. The reagents for the reactions described herein are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the reagents are available from commercial suppliers such as Sigma-Aldrich (Milwaukee, Wisconsin, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (Wiley, 7th Edition), and Larock's Comprehensive Organic Transformations (Wiley-VCH, 1999), and any of available updates as of this filing.

Pharmaceutical Compositions

[0125] Certain embodiments are directed to a pharmaceutical composition comprising one or more compounds of the present disclosure.

[0126] The pharmaceutical composition can optionally contain a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of the present disclosure (e.g., a compound of Formula I (e.g., Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients are known in the art. Non-limiting suitable excipients include, for example, encapsulating materials or additives such as antioxidants, binders, buffers, carriers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. See also Remington's The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, Md., 2005; incorporated herein by reference), which discloses various

excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0127] The pharmaceutical composition can include any one or more of the compounds of the present disclosure. For example, in some embodiments, the pharmaceutical composition comprises a compound of Formula I or a pharmaceutically acceptable salt thereof, e.g., in a therapeutically effective amount. In any of the embodiments described herein, the pharmaceutical composition can comprise a therapeutically effective amount (e.g., for treating an autoimmune and/or inflammatory disease or disorder herein) of a compound selected from any of Examples 1-174, or any of the specific compounds disclosed in Table 1 herein, or a pharmaceutically acceptable salt thereof. In some preferred embodiments, the pharmaceutical composition can comprise a compound selected from the compounds according to Examples 1-174 that have an IC₅₀ value less than 100 nM, more preferably, less than 50 nM, as measured according to Biological Example 1.

[0128] The pharmaceutical composition herein can be formulated for delivery via any of the known routes of delivery, which include but not limited to administering orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally or parenterally.

[0129] In some embodiments, the pharmaceutical composition can be formulated for oral administration. The oral formulations can be presented in discrete units, such as capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Excipients for the preparation of compositions for oral administration are known in the art. Non-limiting suitable excipients include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium

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lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof.

[0130] In some embodiments, the pharmaceutical composition is formulated for parenteral administration (such as intravenous injection or infusion, subcutaneous or intramuscular injection). The parenteral formulations can be, for example, an aqueous solution, a suspension, or an emulsion. Excipients for the preparation of parenteral formulations are known in the art. Non-limiting suitable excipients include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof.

[0131] Compounds of the present disclosure can be used alone, in combination with each other, or in combination with one or more additional therapeutic agents. When used in combination with one or more additional therapeutic agents, compounds of the present disclosure or pharmaceutical compositions herein can be administered to the subject either concurrently or sequentially in any order with such additional therapeutic agents. In some embodiments, the pharmaceutical composition can comprise one or more compounds of the present disclosure and the one or more additional therapeutic agents in a single composition. In some embodiments, the pharmaceutical composition comprising one or more compounds of the present disclosure can be included in a kit which also comprises a separate pharmaceutical composition comprising the one or more additional therapeutic agents.

[0132] The pharmaceutical composition can include various amounts of the compounds of the present disclosure, depending on various factors such as the intended use and potency and selectivity of the compounds. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of the present disclosure. In some embodiments, the pharmaceutical composition comprises a therapeutically effective amount of the compound of the present disclosure and a pharmaceutically acceptable excipient. As used herein, a therapeutically effective amount of a compound of the present disclosure is an amount effective to treat a disease or disorder as described herein, such as an autoimmune and/or inflammatory disease or disorder herein, such as psoriasis, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration,

the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

Method of Treatment/Use

[0133] Compounds of the present disclosure have various utilities. For example, compounds of the present disclosure can be used as therapeutic active substances for the treatment and/or prophylaxis of a disease or disorder associated with IL-17A and/or IL-17F, more particularly, those associated with IL-17A, such as with IL-17AA or IL-17 AF. Accordingly, some embodiments of the present disclosure are also directed to methods of using one or more compounds of the present disclosure or pharmaceutical compositions herein for treating or preventing a disease or disorder associated with IL-17A and/or IL-17F in a subject in need thereof, such as for treating an autoimmune disease or disorder or an inflammatory disease or disorder in a subject in need thereof.

[0134] In some embodiments, the present disclosure provides a method of modulating IL-17A and/or IL-17F in a subject in need thereof, comprising administering to the subject one or more compounds of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein.

[0135] In some embodiments, the present disclosure provides a method of treating or preventing a disease or disorder that is mediated by IL-17A and/or IL-17F in a subject in need thereof, comprising administering to the subject one or more compounds of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein. Such diseases include inflammatory diseases and disorders, proliferative diseases (e.g., cancer), autoimmune diseases and other diseases described herein.

[0136] In some embodiments, the present disclosure provides a method of a method of treating an inflammatory disease or disorder in a subject in need thereof, comprising administering to the subject one or more compounds of the present disclosure (e.g., a

compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein. In some embodiments, the inflammatory disease or disorder is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.

[0137] In some embodiments, the present disclosure provides a method of a method of treating an autoimmune disease or disorder in a subject in need thereof, comprising administering to the subject one or more compounds of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein. In some embodiments, the autoimmune disease or disorder is psoriasis, psoriatic arthritis or ankylosing spondylitis. In some embodiments, the autoimmune disease or disorder is psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, bone erosion, allograft rejection, or multiple sclerosis.

[0138] In some embodiments, the present disclosure provides a method of a method of treating psoriasis in a subject in need thereof, comprising administering to the subject one or more compounds of the present disclosure (e.g., a compound of Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, any of the compounds listed in Table 1 herein, or a pharmaceutically acceptable salt thereof) or a pharmaceutical composition herein.

[0139] The compound of the present disclosure can be used alone or in combination with one or more additional therapeutic agents. When used in combination with one or more additional therapeutic agents, the compounds of the present disclosure or pharmaceutical compositions herein can be administered to the subject either concurrently or sequentially in any order with such additional therapeutic agents.

[0140] Dosing regimen including doses for the methods described herein can vary and be adjusted, which can depend on the recipient of the treatment, the disorder, condition or disease being treated and the severity thereof, the composition containing the compound, the time of administration, the route of administration, the duration of treatment, the compound potency, its rate of clearance and whether or not another drug is co-administered.

Definitions

[0141] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof.

[0142] It is also meant to be understood that a specific embodiment of a variable moiety herein can be the same or different as another specific embodiment having the same identifier.

[0143] Suitable groups for the variables in compounds of Formula I, or a subformula thereof, as applicable, are independently selected. Non-limiting useful groups for the variables in compounds of Formula I, or a subformula thereof, as applicable, include any of the respective groups, individually or in any combination, as shown in the Examples or in the specific compounds described in Table 1 herein. In addition, it is to be understood that the definition of a variable in Formula I can have the same definition for the variable defined in a subformula of Formula I. Similarly, unless otherwise specified or contrary from context, the definition of a subformula of Formula I can have the same definition for the variable defined in connection with Formula I or another subformula of Formula I.

[0144] The described embodiments of the present disclosure can be combined. Such combination is contemplated and within the scope of the present disclosure. For example, it is contemplated that the definition(s) of any one or more of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , Y, Z, Ring A, and n of Formula I can be combined with the definition of any one or more of the other(s) of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , Y, Z, Ring A, and n, as applicable, and the resulted compounds from the combination are contemplated and within the scope of the present disclosure.

[0145] The symbol, , when displayed perpendicular to (or otherwise crossing) a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule. It should be noted that for a divalent structure (or multivalent structure), the immediately connected group or groups or appropriate variable(s) shown in a formula may be shown in the divalent structure (or multivalent structure) beyond the symbol, , to indicate direction

of attachment. When the immediately connected group(s) or variable is not shown for either of the two attaching points of a divalent structure, it should mean that either direction of attachment to the remainder of the molecule is allowed, unless otherwise specified or obviously contrary from context. Direction of attachment for divalent structures herein may also be shown by specifying that one of the attaching point (or variable) is attached/linked/bonded to another attaching point (or variable) in a structure herein, or by specifying the relative positions (e.g., ortho, meta, para, etc.) of one group (or variable) to another group (or variable) in a structure herein.

[0146] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents described herein.

[0147] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high performance liquid chromatography (HPLC), chiral supercritical fluid chromatography (SFC), and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds

described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers including racemic mixtures. When a stereochemistry is specifically drawn, unless otherwise contradictory from context, it should be understood that with respect to that particular chiral center or axial chirality, the compound can exist predominantly as the as-drawn stereoisomer, such as with less than 20%, less than 10%, less than 5%, less than 1%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount of the other stereoisomer(s), for example, the compound can have an enantiomeric excess of greater than 60%, greater than 80%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. The presence and/or amounts of stereoisomers can be determined by those skilled in the art in view of the present disclosure, including through the use of a chiral HPLC or chiral SFC. As understood by those skilled in the art, when a "*" is shown in the chemical structures herein, unless otherwise contradictory from context, it is to designate that the corresponding chiral center is enantiomerically pure or enriched in either of the configurations or is enantiomerically pure or enriched in the as-drawn configuration, such as with less than 20%, less than 10%, less than 5%, less than 1%, by weight, by HPLC or SFC area, or both, or with a non-detectable amount of the other stereoisomer(s). Also, when no stereochemistry is specifically drawn, and no "*" is used in the chemical structures, unless otherwise contradictory from context, it should be understood that such structures include the corresponding compound in any stereoisomeric forms, including individual isomers substantially free of other isomers and mixtures of various isomers including racemic mixtures.

[0148] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁₋₆" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆.

[0149] As used herein, the term "compound(s) of the present disclosure" refers to any of the compounds described herein according to Formula I (e.g., Formula I-E1, I-A, I-A-1, I-A-2, I-A-3, I-1, I-2, I-3, I-4, I-1a, I-1b, I-1b-1, I-1c, I-1c-1, I-1d, I-1d-1, I-4a, I-4a-1, I-4a-2, I-4-D2, I-4a-D2, I-4a-1-D2, or I-4a-2-D2), any of Examples 1-174, or any of the specific compounds disclosed in Table 1 herein, isotopically labeled compound(s) thereof (such as a deuterated analog wherein one or more of the hydrogen atoms is/are substituted with a deuterium atom with an abundance above its natural abundance, e.g., a CD₃ analog when the compound has a CH₃ group), possible regioisomers, possible geometric isomers, possible stereoisomers

thereof (including diastereoisomers, enantiomers, and racemic mixtures), tautomers thereof, conformational isomers thereof, pharmaceutically acceptable esters thereof, and/or possible pharmaceutically acceptable salts thereof (e.g., acid addition salt such as HCl salt or base addition salt such as Na salt). Hydrates and solvates of the compounds of the present disclosure are considered compositions of the present disclosure, wherein the compound(s) is in association with water or solvent, respectively.

[0150] Compounds of the present disclosure can exist in isotope-labeled or -enriched form containing one or more atoms having an atomic mass or mass number different from the atomic mass or mass number most abundantly found in nature. Isotopes can be radioactive or non-radioactive isotopes. Isotopes of atoms such as hydrogen, carbon, phosphorous, sulfur, fluorine, chlorine, and iodine include, but are not limited to ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I . Compounds that contain other isotopes of these and/or other atoms are within the scope of this invention.

[0151] As used herein, the phrase "administration" of a compound, "administering" a compound, or other variants thereof means providing the compound or a prodrug of the compound to the individual in need of treatment.

[0152] As used herein, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic saturated hydrocarbon. In some embodiments, the alkyl can include one to twelve carbon atoms (i.e., C_{1-12} alkyl) or the number of carbon atoms designated. In one embodiment, the alkyl group is a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-10} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is a straight chain C_{1-4} alkyl group. For example, a C_{1-4} alkyl group includes methyl, ethyl, propyl (n-propyl), isopropyl, butyl (n-butyl), sec-butyl, tert-butyl, and iso-butyl. As used herein, the term "alkylene" as used by itself or as part of another group refers to a divalent radical derived from an alkyl group, i.e., by removing any one hydrogen from the alkyl group. For example, non-limiting straight chain alkylene groups (i.e., $(\text{CH}_2)_x$) include $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, and the like.

[0153] As used herein, the term "alkenyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, for example, one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a

C₂₋₆ alkenyl group. In another embodiment, the alkenyl group is a C₂₋₄ alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl, pentenyl, and hexenyl.

[0154] As used herein, the term "alkynyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one or more, for example, one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-carbon triple bond. In one embodiment, the alkynyl group is a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is a C₂₋₄ alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butyne, pentynyl, and hexynyl groups.

[0155] As used herein, the term "alkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein R^{a1} is an alkyl.

[0156] As used herein, the term "cycloalkoxy" as used by itself or as part of another group refers to a radical of the formula OR^{a1}, wherein R^{a1} is a cycloalkyl.

[0157] As used herein, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more fluorine, chlorine, bromine and/or iodine atoms. In preferred embodiments, the haloalkyl is an alkyl group substituted with one, two, or three fluorine atoms. In one embodiment, the haloalkyl group is a C₁₋₁₀ haloalkyl group. In one embodiment, the haloalkyl group is a C₁₋₆ haloalkyl group. In one embodiment, the haloalkyl group is a C₁₋₄ haloalkyl group.

[0158] As used herein, the term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched-chain alkyl group, e.g., having from 2 to 14 carbons, such as 2 to 10 carbons in the chain, in which one or more of the carbons has been replaced by a heteroatom selected from S, O, P and N, and wherein the nitrogen, phosphine, and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) S, O, P and N may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. When the heteroalkyl is said to be substituted, the substituent(s) can replace one or more hydrogen atoms attached to the carbon atom(s) and/or the heteroatom(s) of the heteroalkyl. In some embodiments, the heteroalkyl is a C₁₋₄ heteroalkyl, which refers to the heteroalkyl defined herein having 1-4 carbon atoms. Examples of C₁₋₄ heteroalkyl include, but are not limited to, C₄ heteroalkyl such as -CH₂-CH₂-N(CH₃)-CH₃, C₃ heteroalkyl such as -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-

S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, C₂ heteroalkyl such as -CH₂-CH₂-OH, -CH₂-CH₂-NH₂, -CH₂-NH(CH₃), -O-CH₂-CH₃ and C₁ heteroalkyl such as, -CH₂-OH, -CH₂-NH₂, -O-CH₃. Preferably, the C₁₋₄ heteroalkyl (or C₁₋₄ heteroalkylene) herein contains 1 or 2 heteroatoms, such as one oxygen, one nitrogen, two oxygens, two nitrogens, or one oxygen and one nitrogen. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-O-CH₂-CH₂- and -O-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

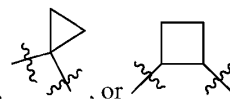
[0159] In some preferred embodiments, unless otherwise specified or contrary from context, a C₁₋₆ heteroalkyl herein can be a C₁₋₆ alkoxy, NH(C₁₋₆ alkyl), N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-O-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-NH(C₁₋₅ alkyl), -(C₁₋₄ alkylene)-N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-S-(C₁₋₅ alkyl), -(C₁₋₅ alkylene)-SO₂-(C₁₋₅ alkyl), SO₂(C₁₋₆ alkyl), P(O)(C₁₋₄ alkyl)(C₁₋₄ alkyl), SO₂NH(C₁₋₆ alkyl), SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -(C₁₋₅ alkylene)-SO₂NH-(C₁₋₅ alkyl), or -(C₁₋₄ alkylene)-SO₂N(C₁₋₄ alkyl)(C₁₋₄ alkyl), provided that the total number of carbons are no greater than 6, not counting any optional substituents. In some preferred embodiments, a C₁₋₆ heteroalkylene herein can be derived from any of the foregoing C₁₋₆ heteroalkyl groups by removing one hydrogen atom.

[0160] In some preferred embodiments, unless otherwise specified or contrary from context, a C₁₋₄ heteroalkyl herein can be a C₁₋₄ alkoxy, NH(C₁₋₄ alkyl), N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-O-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-NH(C₁₋₃ alkyl), -(C₁₋₂ alkylene)-N(C₁₋₂ alkyl)(C₁₋₂ alkyl), -(C₁₋₃ alkylene)-S-(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂-(C₁₋₃ alkyl), SO₂(C₁₋₄ alkyl), P(O)(C₁₋₃ alkyl)(C₁₋₃ alkyl), SO₂NH(C₁₋₄ alkyl), SO₂N(C₁₋₃ alkyl)(C₁₋₃ alkyl), -(C₁₋₃ alkylene)-SO₂NH-(C₁₋₃ alkyl), or -(C₁₋₂ alkylene)-SO₂N(C₁₋₂ alkyl)(C₁₋₂ alkyl), provided that the total number of carbons are no greater than 4, not counting any optional substituents. In some

preferred embodiments, a C₁₋₄ heteroalkylene herein can be derived from any of the foregoing C₁₋₄ heteroalkyl groups by removing one hydrogen atom.

[0161] “Carbocyclyl” or “carbocyclic” as used by itself or as part of another group refers to a radical of a non-aromatic cyclic hydrocarbon group having at least 3 carbon atoms, e.g., from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”), and zero heteroatoms in the non-aromatic ring system. The carbocyclyl group can be either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be partially unsaturated. Non-limiting exemplary carbocyclyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclopentenyl, and cyclohexenyl. As used herein, the term “carbocyclylene” as used by itself or as part of another group refers to a divalent radical derived from the carbocyclyl group defined herein.

[0162] In some embodiments, “carbocyclyl” is fully saturated, which is also referred to as cycloalkyl. In some embodiments, the cycloalkyl can have from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In preferred embodiments, the cycloalkyl is a monocyclic ring. As used herein, the term “cycloalkylene” as used by itself or as part of another group refers to a



divalent radical derived from a cycloalkyl group, for example, , or , etc.

[0163] Unless otherwise defined or contrary from context, a heteroatom herein refers to an atom selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. More preferably, a heteroatom herein refers to an atom selected from nitrogen, oxygen, and sulfur.

[0164] “Heterocyclyl” or “heterocyclic” as used by itself or as part of another group refers to a radical of a 3-membered or larger, such as 3- to 14-membered, non-aromatic ring system having ring carbon atoms and at least one ring heteroatom, such as 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged, or spiro ring system, such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. When all ring carbon atoms in a heterocyclyl as defined herein are saturated carbons, then the heterocyclyl may also be referred to as a heterocycloalkyl.

Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings,

and the point of attachment can be on any ring. As used herein, the term "heterocyclylene" as used by itself or as part of another group refers to a divalent radical derived from the heterocyclyl group defined herein. The heterocyclyl or heterocyclylene can be optionally linked to the rest of the molecule through a carbon or nitrogen atom.

[0165] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as an example of a 5,6-bicyclic heterocyclic ring) include, without limitation, indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as an example of a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinoliny, tetrahydroisoquinoliny, and the like.

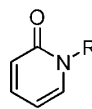
[0166] "Aryl" as used by itself or as part of another group refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C₆₋₁₄ aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C₆ aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten

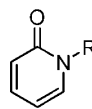
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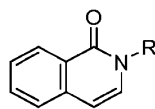
ring carbon atoms ("C₁₀ aryl"; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C₁₄ aryl"; *e.g.*, anthracyl). As used herein, the term "arylene" as used by itself or as part of another group refers to a divalent radical derived from the aryl group defined herein.

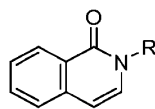
[0167] "Aralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more aryl groups, preferably, substituted with one aryl group. Examples of aralkyl include benzyl, phenethyl, etc. When an aralkyl is said to be optionally substituted, either the alkyl portion or the aryl portion of the aralkyl can be optionally substituted.

[0168] "Heteroaryl" as used by itself or as part of another group refers to a radical of a 5–14 membered monocyclic, bicyclic, or tricyclic 4n+2 aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and at least one, preferably, 1–4, ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–14 membered heteroaryl"). As



used herein, for clarity, a pyridone (*e.g.*, a pyridin-2-one, , wherein R can be hydrogen or a nitrogen atom substituent), pyrimidinone, or the like, such as a pyridone fused



to an aryl or heteroaryl (*e.g.*, , wherein R can be hydrogen or a nitrogen atom substituent), is considered a heteroaryl ring herein. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. In bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolyl, and the like), the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). As used herein, the term "heteroarylene" as used by itself or as part of another group refers to a divalent radical derived from the heteroaryl group defined herein.

[0169] Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and

thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiopinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalyl, phthalazinyl, and quinazolinyl.

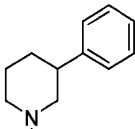
[0170] "Heteroaralkyl" as used by itself or as part of another group refers to an alkyl substituted with one or more heteroaryl groups, preferably, substituted with one heteroaryl group. When a heteroaralkyl is said to be optionally substituted, either the alkyl portion or the heteroaryl portion of the heteroaralkyl can be optionally substituted.

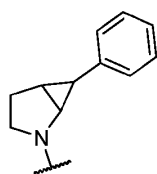
[0171] As used herein, unless specified or otherwise contrary, a "ring structure", "cyclic structure", or simply "ring", with a designated number of ring members, such as a "3-10 membered ring structure", a "3-12 membered ring structure", or a "5- or 6-membered ring", should be understood as encompassing any ring structure (e.g., carbocyclic, heterocyclic, aryl, heteroaryl, etc.) having the designated number of ring members, which can be (1) monocyclic or polycyclic (as chemically feasible), such as a monocyclic ring or a bicyclic ring (including fused, spiro, and bridged bicyclic ring, and those ring systems where two monocyclic rings are connected through a single or double bond); (2) aromatic, partially unsaturated, or fully saturated; and in the case of a polycyclic structure, each ring can be independently aromatic, partially unsaturated, or fully saturated; and (3) containing no heteroatom (i.e., all ring members are carbon atoms) or 1-4 heteroatoms; or in the case of a polycyclic structure, each ring can independently have no ring heteroatom or 1-4 ring heteroatoms (e.g., O, N, S, etc.). When a ring is said to contain a ring sulfur or nitrogen atom, the sulfur or nitrogen atom can be optionally oxidized. One or more ring carbon atoms in a ring structure can be present as C(=O). A fully saturated ring refers to a ring in which

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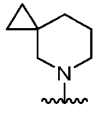
none of the ring carbon atom(s) and any present ring heteroatom(s) (e.g., nitrogen) forms a double bond or triple bond with any other atom. The ring structure can be optionally substituted with one or more substituents described herein. The substituents of a ring structure herein can also have a cyclic structure, and in some cases, two substituents of a ring structure may be said to be joined to form a cyclic structure.

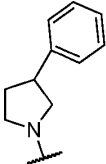
[0172] As commonly understood in the art, for clarity, when a structure can be characterized in multiple ways, as long as one such characterization falls within the scope of the definition of a variable herein, it can be said that the structure is a suitable definition for the variable. For example, when a monovalent variable is defined as an optionally substituted 6-membered

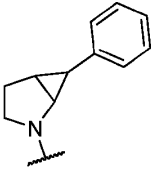
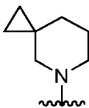
ring, the variable encompasses, among other structures, (a) the structure of  or



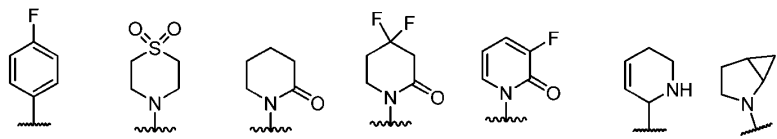
, which can be viewed as a 6-membered monocyclic or bicyclic ring

substituted with a phenyl group; and (b) the structure of , which can be viewed as a 6-membered ring, wherein two substituents are joined to form a cyclopropyl ring (unless the optional substituents for the 6-membered ring are specified and do not include this as an

option); but the variable would not encompass  because the attaching ring is not a 6-membered ring under any characterization of the structure. To further explain, when the variable is instead defined as an optionally substituted monocyclic 6-membered ring, then the

variable does not encompass , but encompasses the structure of .

(unless the optional substituents for the 6-membered ring are specified and do not include this as an option). And if the variable is defined as a 6-membered ring optionally substituted with halogen, then the variable can encompass structures such as,



as each of which can be viewed as a 6-membered ring that is unsubstituted or substituted with 1 or two fluorine atoms.

[0173] As commonly understood in the art, alkylene, alkenylene, alkynylene, heteroalkylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene refer to the corresponding divalent radicals of alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, respectively.

[0174] An “optionally substituted” group, such as an optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl groups, refers to the respective group that is unsubstituted or substituted. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent can be the same or different at each position. Typically, when substituted, the optionally substituted groups herein can be substituted with 1-5 substituents. Substituents can be a carbon atom substituent, a nitrogen atom substituent, an oxygen atom substituent or a sulfur atom substituent, as applicable, each of which can be optionally isotopically labeled, such as deuterated. Two of the optional substituents can join to form a ring structure, such as an optionally substituted cycloalkyl, heterocyclyl, aryl, or heteroaryl ring. Substitution can occur on any available carbon, oxygen, or nitrogen atom, and can form a spirocycle. Typically, substitution herein does not result in an O-O, O-N, S-S, S-N (except SO₂-N bond), heteroatom-halogen, or -C(O)-S bond or three or more consecutive heteroatoms, with the

exception of O-SO₂-O, O-SO₂-N, and N-SO₂-N, except that some of such bonds or connections may be allowed if in a stable aromatic system.

[0175] In a broad aspect, the permissible substituents herein include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a cycloalkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a heterocyclyl, an aralkyl, an aryl, or a heteroaryl, each of which can be substituted, if appropriate.

[0176] Exemplary substituents include, but not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, -alkylene-aryl, -arylene-alkyl, -alkylene-heteroaryl, -alkenylene-heteroaryl, -alkynylene-heteroaryl, —OH, hydroxyalkyl, haloalkyl, —O-alkyl, —O-haloalkyl, -alkylene-O-alkyl, —O-aryl, —O-alkylene-aryl, —O-heteroaryl, —O-alkylene-heteroaryl, —O-cycloalkyl, —O-heterocycloalkyl, acyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)-aryl, —C(O)-alkylene-aryl, —C(O)-heteroaryl, —C(O)-alkylene-heteroaryl, —C(O)-cycloalkyl, —C(O)-heterocycloalkyl, halo, —NO₂, —CN, —SF₅, —C(O)OH, —C(O)O-alkyl, —C(O)O-aryl, —C(O)O-alkylene-aryl, —S(O)-alkyl, —S(O)₂-alkyl, —S(O)-haloalkyl, —S(O)₂-haloalkyl, —S(O)-aryl, —S(O)₂-aryl, —S(O)-heteroaryl, —S(O)₂-heteroaryl, —S-alkyl, —S-aryl, —S-heteroaryl, —S-alkylene-aryl, —S-alkylene-heteroaryl, —S(O)₂-alkylene-aryl, —S(O)₂-alkylene-heteroaryl, —S-cycloalkyl, —S-heterocycloalkyl, —S(O)-cycloalkyl, —S(O)-heterocycloalkyl, —S(O)₂-cycloalkyl, —S(O)₂-heterocycloalkyl, —S(O)(=NH)-alkyl, —S(O)(=NH)-haloalkyl, —S(O)(=NH)-aryl, —S(O)(=NH)-alkylene-aryl, —S(O)(=NH)-heteroaryl, —S(O)(=NH)-alkylene-heteroaryl, —S(O)(=NH)-cycloalkyl, —S(O)(=NH)-heterocycloalkyl, —S(O)(=Nalkyl)-alkyl, —S(O)(=Nalkyl)-haloalkyl, —S(O)(=Nalkyl)-aryl, —S(O)(=Nalkyl)-alkylene-aryl, —S(O)(=Nalkyl)-heteroaryl, —S(O)(=Nalkyl)-

alkylene-heteroaryl, —S(O)(=Nalkyl)-cycloalkyl, —S(O)(=Nalkyl)-heterocycloalkyl, cycloalkyl, heterocycloalkyl, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, —C(=N—CN)—NH₂, —C(=NH)—NH₂, —C(=NH)—NH(alkyl), —N(Y₁)(Y₂), -alkylene-N(Y₁)(Y₂), —C(O)N(Y₁)(Y₂) and —S(O)₂N(Y₁)(Y₂), wherein Y₁ and Y₂ can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, cycloalkyl, heterocycloalkyl, and Y₁ and Y₂ with the nitrogen they linked can form a heterocyclic ring.

[0177] Some examples of suitable substituents include, but not limited to, (C₁-C₈)alkyl groups, (C₂-C₈)alkenyl groups, (C₂-C₈)alkynyl groups, (C₃-C₁₀)cycloalkyl groups, halogen (F, Cl, Br or I), halogenated (C₁-C₈)alkyl groups (for example but not limited to —CF₃), —O—(C₁-C₈)alkyl groups, —OH, —S—(C₁-C₈)alkyl groups, —SH, —NH(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)₂ groups, —NH₂, —C(O)NH₂, —C(O)NH(C₁-C₈)alkyl groups, —C(O)N((C₁-C₈)alkyl)₂, —NHC(O)H, —NHC(O)(C₁-C₈)alkyl groups, —NHC(O)(C₃-C₈)cycloalkyl groups, —N((C₁-C₈)alkyl)C(O)H, —N((C₁-C₈)alkyl)C(O)(C₁-C₈)alkyl groups, —NHC(O)NH₂, —NHC(O)NH(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)C(O)NH₂ groups, —NHC(O)N((C₁-C₈)alkyl)₂ groups, —N((C₁-C₈)alkyl)C(O)N((C₁-C₈)alkyl)₂ groups, —N((C₁-C₈)alkyl)C(O)NH((C₁-C₈)alkyl), —C(O)H, —C(O)(C₁-C₈)alkyl groups, —CN, —NO₂, —S(O)(C₁-C₈)alkyl groups, —S(O)₂(C₁-C₈)alkyl groups, —S(O)₂N((C₁-C₈)alkyl)₂ groups, —S(O)₂NH(C₁-C₈)alkyl groups, —S(O)₂NH(C₃-C₈)cycloalkyl groups, —S(O)₂NH₂ groups, —NHS(O)₂(C₁-C₈)alkyl groups, —N((C₁-C₈)alkyl)S(O)₂(C₁-C₈)alkyl groups, —(C₁-C₈)alkyl-O—(C₁-C₈)alkyl groups, —O—(C₁-C₈)alkyl-O—(C₁-C₈)alkyl groups, —C(O)OH, —C(O)O(C₁-C₈)alkyl groups, NHOH, NHO(C₁-C₈)alkyl groups, —O-halogenated (C₁-C₈)alkyl groups (for example but not limited to —OCF₃), —S(O)₂-halogenated (C₁-C₈)alkyl groups (for example but not limited to —S(O)₂CF₃), —S-halogenated (C₁-C₈)alkyl groups (for example but not limited to —SCF₃), —(C₁-C₆) heterocycle (for example but not limited to pyrrolidine, tetrahydrofuran, pyran or morpholine), —(C₁-C₆) heteroaryl (for example but not limited to tetrazole, imidazole, furan, pyrazine or pyrazole), -phenyl, —NHC(O)O—(C₁-C₆)alkyl groups, —N((C₁-C₆)alkyl)C(O)O—(C₁-C₆)alkyl groups, —C(=NH)—(C₁-C₆)alkyl groups, —C(=NOH)—(C₁-C₆)alkyl groups, or —C(=N—O—(C₁-C₆)alkyl)-(C₁-C₆)alkyl groups.

[0178] Exemplary carbon atom substituents include, but are not limited to, deuterium, halogen, —CN, —NO₂, —N₃, hydroxyl, alkoxy, cycloalkoxy, aryloxy, amino, monoalkyl amino,

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dialkyl amino, amide, sulfonamide, thiol, acyl, carboxylic acid, ester, sulfone, sulfoxide, alkyl, haloalkyl, alkenyl, alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl, etc. For example, exemplary carbon atom substituents can include F, Cl, -CN, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -NH₂, -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), -SH, -SC₁₋₆ alkyl, -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -NHCO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal substituents can be joined to form =O.

[0179] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, acyl groups, esters, sulfone, sulfoxide, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two substituent groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, incorporated by reference herein. Exemplary nitrogen protecting groups include, but not limited to, those forming carbamates, such as Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonyl (Moz or MeOZ) group, tert-Butyloxycarbonyl (BOC) group, Troc, 9-Fluorenylmethyloxycarbonyl (Fmoc) group, etc., those forming an amide, such as acetyl, benzoyl, etc., those forming a benzylic amine, such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, etc., those forming a sulfonamide, such as tosyl, Nosyl, etc., and others such as p-methoxyphenyl.

[0180] Exemplary oxygen atom substituents include, but are not limited to, acyl groups, esters, sulfonates, C₁₋₁₀ alkyl, C₁₋₁₀ haloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl,

3–14 membered heterocyclyl, C_{6–14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl can be further substituted as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protective Groups in Organic Synthesis*, 4th ed. P. G. M. Wuts; T. W. Greene, John Wiley, 2007, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, those forming alkyl ethers or substituted alkyl ethers, such as methyl, allyl, benzyl, substituted benzyis such as 4-methoxybenzyl, methoxymethyl (MOM), benzyloxymethyl (BOM), 2-methoxyethoxymethyl (MEM), etc., those forming silyl ethers, such as trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), t-butyl dimethylsilyl (TBDMS), etc., those forming acetals or ketals, such as tetrahydropyranyl (THP), those forming esters such as formate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, etc., those forming carbonates or sulfonates such as methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts), etc.

[0181] Unless expressly stated to the contrary, combinations of substituents and/or variables are allowable only if such combinations are chemically allowed and result in a stable compound. A “stable” compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject).

[0182] Unless otherwise specified or contrary from context, the optionally substituted groups as defined in connection with Formula I can be (A) unsubstituted; (B) substituted with one or more substituents each independently deuterium, halogen, CN, or Y¹-Y²-Y³-Y⁴, wherein Y¹, Y², and Y³ are each independently null, O, NY⁴, C(O), S, SO, SO₂, S(O)(=NY⁴), C_{1–4} alkylene optionally substituted with deuterium, F, and/or OH, or P(O)Y⁴, wherein Y⁴ at each occurrence is independently hydrogen, C_{1–6} alkyl optionally substituted with one or more Y¹⁰, C_{2–6} alkenyl optionally substituted with one or more Y¹⁰, C_{2–6} alkynyl optionally substituted with one or more Y¹⁰, C_{1–6} heteroalkyl optionally substituted with one or more Y¹⁰, or 3–14 membered ring optionally substituted with one or more Y¹⁰, wherein Y¹⁰ at each occurrence is independently deuterium, halogen, oxo (as applicable), CN, or Y²⁰-Y²¹-Y²²-Y²³, wherein Y²⁰, Y²¹, and Y²² are each independently null, O, NY²³, C(O), S, SO, SO₂, S(O)(=NY²³), C_{1–4}

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alkylene optionally substituted with deuterium, F, and/or OH, or P(O)Y²³, wherein Y²³ at each occurrence is independently hydrogen, C₁₋₆ alkyl optionally substituted with one or more Y³⁰, C₂₋₆ alkenyl optionally substituted with one or more Y³⁰, C₂₋₆ alkynyl optionally substituted with one or more Y³⁰, C₁₋₆ heteroalkyl optionally substituted with one or more Y³⁰, or 3-8 membered ring optionally substituted with one or more Y³⁰, wherein Y³⁰ at each occurrence is independently deuterium, halogen, oxo (as applicable), CN, OH, NH₂, C₁₋₄ alkyl optionally substituted with one or more Y³¹, C₁₋₄ heteroalkyl optionally substituted with one or more Y³¹, or 3-5 membered ring optionally substituted with one or more Y³¹, wherein Y³¹ at each occurrence is independently deuterium, F, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ heteroalkyl optionally substituted with deuterium and/or F; or (C) two or more substituents of the respective optionally substituted group, and/or one of the substituents of the respective optionally substituted group and another variable herein, are joined to form a ring (e.g., a spiro ring, a fused ring, or a bridged ring), which is optionally substituted with one or more substituents as defined in (B), and any remaining substituents of the respective optionally substituted group are as defined in (B). In some preferred embodiments, the optionally substituted groups as defined in connection with Formula I can be unsubstituted or substituted with one or more substituents as defined in (B). The combination of Y¹, Y², and Y³ is not particularly limited, which can preferably be (a) a linker of O, NY⁴, C(O), S, SO, SO₂, or P(O)Y⁴, when two of Y¹, Y², and Y³ are null, or (b) a linker of amide (C(O)NY⁴), ester (C(O)O), sulfonamide (SO₂NY⁴), etc., when one of Y¹, Y², and Y³ is null, or (c) a linker of carbamate (OC(O)NY⁴), urea (NY⁴C(O)NY⁴), sulfamoylamino (NY⁴SO₂NY⁴), etc., when none of Y¹, Y², and Y³ is null. The combination of Y²⁰, Y²¹, and Y²² should be understood similarly.

[0183] Unless otherwise specified or contrary from context, when a group herein is defined as being optionally substituted with one or more substituents selected from a defined list or simply a defined list of substituents, the group is typically unsubstituted or substituted with 1, 2, 3, or 4 substituents as defined, although in some embodiments, the group can also be substituted with more than 4 substituents. For example, an alkyl group optionally substituted with one or more substituents independently selected from deuterium, F, and OH can be typically unsubstituted or substituted with 1-4 substituents each independently deuterium, F, or OH. Similarly, an alkyl group optionally substituted with deuterium and/or F is typically unsubstituted or substituted with 1-4 substituents each independently deuterium or F.

[0184] Unless otherwise specified or contrary from context, a 3-8 membered ring herein can be a (i) 3-8 membered carbocyclic ring, (ii) 4-8 membered heterocyclic ring having 1-3 ring heteroatoms each independently O, S, and N, wherein the sulfur atom, if present, is optionally oxidized; (iii) phenyl ring; or (iv) a 5 or 6-membered heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N.

[0185] Unless otherwise specified or contrary from context, a 3-5 membered ring herein can be a (i) 3-5 membered carbocyclic ring, e.g., cyclopropyl, cyclobutyl, etc., (ii) 4-5 membered heterocyclic ring having 1-2 ring heteroatoms each independently O, S, and N, wherein the sulfur atom, if present, is optionally oxidized, e.g., oxetane, azetidine, etc.; or (iii) a 5-membered heteroaryl ring having 1-4 ring heteroatoms each independently O, S, and N.

[0186] In some embodiments, the “optionally substituted” alkyl, alkylene, heteroalkyl, heteroalkylene, alkenyl, alkynyl, carbocyclic, carbocyclylene, cycloalkyl, cycloalkylene, alkoxy, cycloalkoxy, heterocyclyl, or heterocyclylene herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, CN, protected hydroxyl, oxo (as applicable), NH₂, protected amino, NH(C₁₋₄ alkyl) or a protected derivative thereof, N(C₁₋₄ alkyl)(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2, or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1, 2, or 3 substituents independently selected from deuterium, F, Cl, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl (e.g., CF₃), C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy. In some embodiments, the “optionally substituted” aryl, arylene, heteroaryl or heteroarylene group herein can each be independently unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from deuterium, F, Cl, -OH, -CN, NH₂, protected amino, NH(C₁₋₄ alkyl) or a protected derivative thereof, N(C₁₋₄ alkyl)(C₁₋₄ alkyl), -S(=O)(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl), C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, phenyl, 5 or 6 membered heteroaryl containing 1, 2 or 3 ring heteroatoms independently selected from O, S, and N, 3-7 membered heterocyclyl containing 1 or 2 ring heteroatoms independently selected from O, S, and N, wherein each of the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkoxy, phenyl, heteroaryl, and heterocyclyl, is optionally substituted with 1,

2, or 3 substituents independently selected from deuterium, F, -OH, oxo (as applicable), C₁₋₄ alkyl, fluoro-substituted C₁₋₄ alkyl, C₁₋₄ alkoxy and fluoro-substituted C₁₋₄ alkoxy.

[0187] "Halo" or "halogen" refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0188] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

[0189] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from tautomerization. The exact ratio of the tautomers depends on several factors, including for example temperature, solvent, and pH. Tautomerizations are known to those skilled in the art. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0190] The term "subject" (alternatively referred to herein as "patient") as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

[0191] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound described herein to a subject in need of such treatment.

[0192] The term "effective amount" refers to that amount of a compound or combination of compounds as described herein that is sufficient to effect the intended application including, but not limited to, prophylaxis or treatment of diseases. A therapeutically effective amount

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may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (e.g., the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, etc. which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells and/or tissues. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0193] As used herein, the singular form “a”, “an”, and “the”, includes plural references unless it is expressly stated or is unambiguously clear from the context that such is not intended.

[0194] The term “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0195] Headings and subheadings are used for convenience and/or formal compliance only, do not limit the subject technology, and are not referred to in connection with the interpretation of the description of the subject technology. Features described under one heading or one subheading of the subject disclosure may be combined, in various embodiments, with features described under other headings or subheadings. Further it is not necessarily the case that all features under a single heading or a single subheading are used together in embodiments.

Examples

[0196] Abbreviations: The abbreviations used in the Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The following shows certain abbreviations used in the Examples section herein.

BAST	bis(2-methoxyethyl)aminosulfur trifluoride
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane

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DIBAL-H	diisobutyl aluminium hydride
DIEA	N,N-diisopropylethylamine
DMEDA	N,N'-Dimethyl-1,2-ethanediamine
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
EDCI	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
Hr(s)	hour(s)
LCMS	liquid chromatography-mass spectrometry
MTBE	methyl tert-butyl ether
PE	petroleum ether
Rt	room temperature
SFC	supercritical fluid chromatography
TBAB	tetrabutylammonium bromide
TMSCN	trimethylsilylcyanide
TMSOTf	trimethylsilyl trifluoromethanesulfonate

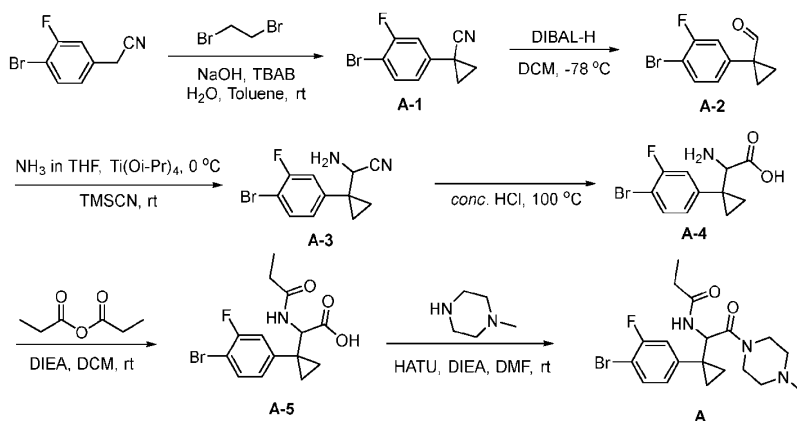
[0197] The various starting materials, intermediates, and compounds of embodiments herein can be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds can be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses. The abbreviations used in the Examples section should be understood as having their ordinary meanings in the art unless specifically indicated otherwise or obviously contrary from context. The examples are illustrative only and do not limit the claimed invention in any way.

[0198] Exemplary embodiments of steps for performing the synthesis of products described herein are described in greater detail infra. Some of the Intermediates and Examples herein have one or more chiral centers. Stereoisomers including enantiomers and diastereomers may be prepared by chiral synthesis and/or chiral resolution. Some of the absolute stereochemistry shown in the Examples section herein (whether or not indicated as tentative) is assigned based on literature or other evidence, or arbitrary assigned. It should be

understood that if the assigned stereochemistry is later found to be incorrect, then the intended structure should be the corresponding compound with the correct stereochemistry. All potential stereoisomers from the synthetic examples are specifically contemplated in this disclosure.

Intermediate A

N-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (A)



Step 1: 1-(4-Bromo-3-fluorophenyl)cyclopropane-1-carbonitrile (A-1)

[0199] To a stirred mixture of 2-(4-bromo-3-fluorophenyl)acetonitrile (5.00 g, 23 mmol) and 1,2-dibromoethane (1.5 mL) in toluene (12.5 mL) was added NaOH (50% in water, 12.5 mL) and TBAB (0.80 g, 2.5 mmol) under N₂. After stirring for 16 hrs at rt under N₂, the mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford 1-(4-bromo-3-fluorophenyl)cyclopropane-1-carbonitrile (5.00 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 (dd, *J* = 8.4 Hz, 7.6 Hz, 1H), 7.29 (dd, *J* = 10.4 Hz, 2.4 Hz, 1H), 7.21 (m, 1H), 1.79 (m, 2H), 1.67-1.55 (m, 2H).

Step 2: 1-(4-Bromo-3-fluorophenyl)cyclopropane-1-carbaldehyde (A-2)

[0200] To a stirred solution of 1-(4-bromo-3-fluorophenyl)cyclopropane-1-carbonitrile (6.30 g, 26 mmol) in DCM (63 mL) was added DIBAL-H (1 M in n-hexane, 52 mL, 52 mmol) dropwise at -78 °C under N₂. After stirring for 1 hr at -78 °C under N₂, the mixture was quenched with water and extracted with DCM. The combined organic layers were washed

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with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1) to afford 1-(4-bromo-3-fluorophenyl)cyclopropane-1-carbaldehyde (4.10 g). ¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1H), 7.53 (dd, *J* = 8.0 Hz, 7.2 Hz, 1H), 7.08 (dd, *J* = 9.2 Hz, 2.0 Hz, 1H), 7.00 (m, 1H), 1.64-1.56 (m, 2H), 1.45-1.37 (m, 2H).

Step 3: 2-Amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetonitrile (A-3)

[0201] To a stirred solution of 1-(4-bromo-3-fluorophenyl)cyclopropane-1-carbaldehyde (4.10 g, 17 mmol) in MeOH (80 mL) was added NH₃ (7 N in MeOH, 24.1 mL, 169 mmol) and Ti(Oi-Pr)₄ (5.75 g, 20 mmol) dropwise at 0 °C under N₂. After stirring for 1 hr at 0 °C under N₂, TMSCN (6.69 g, 67 mmol) was added dropwise at 0 °C. After stirring for an additional 16 hrs at rt, the mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc = 1:1) to afford 2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetonitrile (1.7 g). LCMS (ESI, *m/z*): [M+H]⁺ 269.0.

Step 4: 2-Amino-2-(1-(4-Bromo-3-fluorophenyl)cyclopropyl)acetic acid (A-4)

[0202] A mixture of 2-amino-2-[1-(4-bromo-3-fluorophenyl)cyclopropyl]acetonitrile (1.70 g, 6.3 mmol) in concentrated HCl (20 mL) was stirred for 2 hrs at 100 °C. The resulting mixture was concentrated under reduced pressure to afford the crude product which was used in the next step directly. LCMS (ESI, *m/z*): [M+H]⁺ 288.0.

Step 5: 2-(1-(4-Bromo-3-fluorophenyl)cyclopropyl)-2-propionamidoacetic acid (A-5)

[0203] To a stirred mixture of 2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetic acid (0.80 g, 2.78 mmol) and DIEA (2.15 g, 16.7 mmol) in DCM (10 mL) was added propionic anhydride (1.08 g, 8.33 mmol) dropwise at rt under N₂. After stirring for 1 hr, the mixture was concentrated under reduced pressure to afford the crude product was used in the next step directly. LCMS (ESI, *m/z*): [M+H]⁺ 344.0.

Step 6: N-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (A)

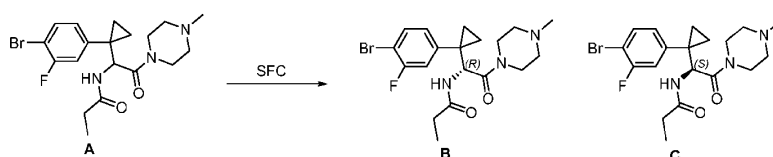
[0204] To a stirred mixture of 2-(1-(4-Bromo-3-fluorophenyl)cyclopropyl)-2-propionamidoacetic acid (0.90 g, 2.62 mmol) and 1-methylpiperazine (0.79 g, 7.84 mmol) in DMF (10 mL) was added HATU (1.99 g, 5.23 mmol) and DIEA (1.35 g, 10.5 mmol) at rt under N₂. After stirring for 16 hrs, the mixture was treated with water and extracted with

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EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (10:1), to afford Intermediate **A** (430 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 426.3.

Intermediates B and C

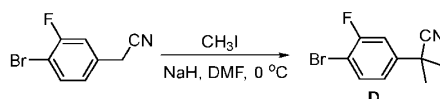
(R)-N-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (B) and (S)-N-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (C)



[0205] The racemate *N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (Intermediate **A**, 180 mg, 0.423 mmol) was purified by SFC with the following conditions (CHIRAL ART Cellulose-SA column, NH_4OH) to afford two separate enantiomers Intermediate **B** (peak 1) and Intermediate **C** (peak 2). Intermediate **B** (peak 1): LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 426.1. Intermediate **C** (peak 2): LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 426.1.

Intermediate D

2-(4-bromo-3-fluorophenyl)-2-methylpropanenitrile (D)

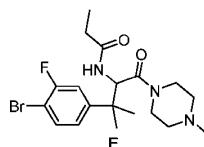


[0206] To a stirred solution of 2-(4-bromo-3-fluorophenyl)acetonitrile (2.00 g, 9.34 mmol) in DMF (20 mL) was added NaH (60 % dispersion in mineral oil, 0.93 g, 23.4 mmol) in portions at 0 °C under N_2 . After stirring for 1 hr at 0 °C, CH_3I (3.32 g, 23.4 mmol) was added dropwise. After stirring for an additional 1 hr, the mixture was quenched with saturated NH_4Cl (aq.) at 0 °C and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford Intermediate **D** (1.00 g). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 242.1.

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Intermediate E

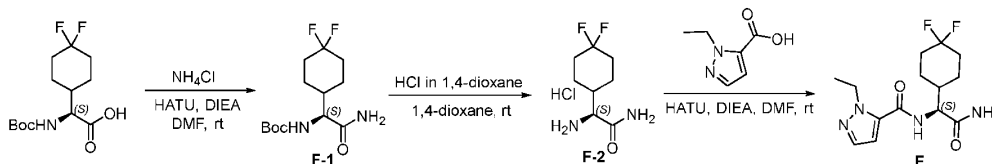
N-(3-(4-bromo-3-fluorophenyl)-3-methyl-1-(4-methylpiperazin-1-yl)-1-oxobutan-2-yl)propionamide (E)



[0207] Following a synthetic sequence analogous to synthesis of **A**, Intermediate **E** was synthesized from **D**. LCMS (ESI, *m/z*): [M+H]⁺ 428.1.

Intermediate F

(S)-N-(2-Amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (F)



Step 1: *tert*-butyl (*S*)-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)carbamate (F-1)

[0208] To a stirred mixture of (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(4,4-difluorocyclohexyl)acetic acid (150 mg, 0.51 mmol) and HATU (292 mg, 0.77 mmol) in DMF (1 mL) was added DIEA (330 mg, 2.6 mmol) and NH₄Cl (32.8 mg, 0.61 mmol) at rt under N₂. After stirring for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product which was used in the next step directly. LCMS (ESI, *m/z*): [M+H]⁺ 237.2.

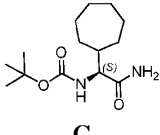
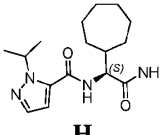
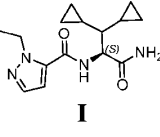
Step 2: (*S*)-2-Amino-2-(4,4-difluorocyclohexyl)acetamide hydrochloride (F-2)

[0209] To a stirred mixture of *tert*-butyl (*S*)-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)carbamate (140 mg, 0.48 mmol) in 1,4-dioxane (0.2 mL) was added HCl solution (4 M in 1,4-dioxane, 1.20 mL) at rt. After stirring for 1 hr, the mixture was concentrated under reduced pressure to afford the crude product as a HCl salt which was used in the next step directly. LCMS (ESI, *m/z*): [M+H]⁺ 193.3.

Step 3: (*S*)-N-(2-Amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (F)

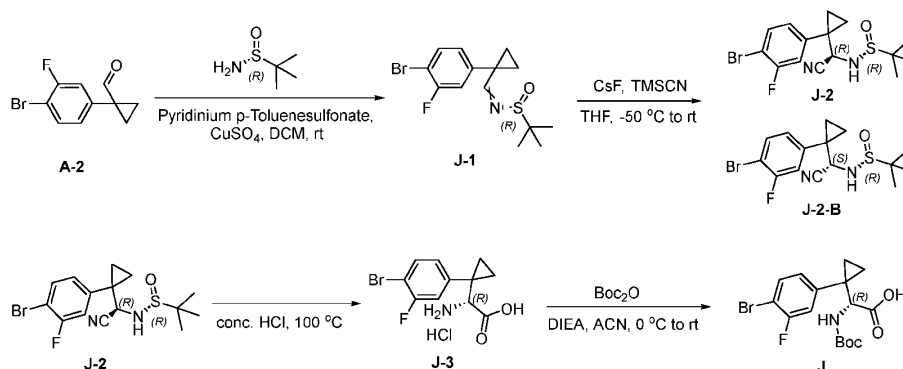
[0210] To a stirred mixture of (*S*)-2-amino-2-(4,4-difluorocyclohexyl)acetamide hydrochloride (130 mg, 0.57 mmol), 2-ethylpyrazole-3-carboxylic acid (87.8 mg, 0.63 mmol) and DIEA (221 mg, 1.7 mmol) in DMF (1.3 mL) was added HATU (325 mg, 0.86 mmol) at rt. After stirring for 2 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc = 1:10) to afford Intermediate **F** (100 mg). LCMS (ESI, *m/z*): [M+H]⁺ 315.3.

[0211] The intermediates in the table below were synthesized using conditions analogous to synthesis of Intermediate **F**.

Intermediates	Name LCMS (ESI, <i>m/z</i>)	Intermediates	Name LCMS (ESI, <i>m/z</i>)
	tert-Butyl (<i>S</i>)-(2-amino-1-cycloheptyl-2-oxoethyl)carbamate [M+H-Boc] ⁺ 171.3		(<i>S</i>)- <i>N</i> -(2-amino-1-cycloheptyl-2-oxoethyl)-1-isopropyl-1 <i>H</i> -pyrazole-5-carboxamide [M+H] ⁺ 307.2
	(<i>S</i>)- <i>N</i> -(1-amino-3,3-dicyclopentyl-1-oxopropan-2-yl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide [M+H] ⁺ 291.3		

Intermediate J

(*R*)-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((*tert*-butoxycarbonyl)amino)acetic acid (**J**)



Step 1: (*R*)-*N*-((1-(4-bromo-3-fluorophenyl)cyclopropyl)methylene)-2-methylpropane-2-sulfinamide (**J-1**)

[0212] To a stirred solution of 1-(4-bromo-3-fluorophenyl)cyclopropane-1-carbaldehyde (9.0 g, 37 mmol) and (*R*)-2-methylpropane-2-sulfinamide (5.8 g, 48 mmol) in DCM (90 mL) were added pyridinium p-toluenesulfonate (1.5 g, 5.9 mmol) and CuSO₄ (23.6 g, 148 mmol) in portions at rt under N₂. After stirring for 16 hrs, the mixture was filtered. The filtrate was washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (3:1), to afford (*R*)-*N*-((1-(4-bromo-3-fluorophenyl)cyclopropyl)methylene)-2-methylpropane-2-sulfinamide (12 g). LCMS (ESI, m/z): [M+H]⁺ 346.1.

Step 2: (*R*)-*N*-((*R*)-(1-(4-bromo-3-fluorophenyl)cyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (**J-2**) & (*R*)-*N*-((*S*)-(1-(4-bromo-3-fluorophenyl)cyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (**J-2-B**)

[0213] To a stirred mixture of (*R*)-*N*-((1-(4-bromo-3-fluorophenyl)cyclopropyl)methylene)-2-methylpropane-2-sulfinamide (10.0 g, 29 mmol) and CsF (4.8 g, 32 mmol) in THF (100 mL) was added TMSCN (3.2 g, 32 mmol) dropwise at -50 °C under N₂. After stirring for 16 hrs at rt, the mixture was treated with saturated NH₄Cl solution and extracted with EtOAc. The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:1), to afford a mixture. The diastereomeric mixture was separated by prep-Achiral-HPLC with the following conditions (Column: DAICEL DCpak P4VP 5*25 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (1%-2 M-NH₃-MeOH); Flow rate: 140 mL/min; Gradient: isocratic 26% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford peak 1 as (*R*)-*N*-((*S*)-(1-(4-bromo-3-fluorophenyl)cyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (**J-2-B**, 2.6 g) and peak 2 as (*R*)-*N*-((*R*)-(1-(4-bromo-3-fluorophenyl)cyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (**J-2**, 5.7 g). LCMS (ESI, m/z): [M+H]⁺ 373.1.

Step 3: (*R*)-2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetic acid hydrochloride (**J-3**)

[0214] A solution of (*R*)-*N*-((*R*)-(1-(4-bromo-3-fluorophenyl)cyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (4.4 g, 12 mmol) in concentrated hydrochloric acid (40 mL) was stirred for 16 hrs at 100 °C under N₂. The mixture was concentrated under reduced pressure to afford (*R*)-2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetic acid as a HCl salt (4.2 g). LCMS (ESI, m/z): [M+H]⁺ 288.1.

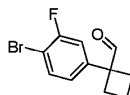
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Step 4: (R)-2-(1-(4-Bromo-3-fluorophenyl)cyclopropyl)-2-((tert-butoxycarbonyl)amino)acetic acid (J)

[0215] To a stirred solution of (R)-2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)acetic acid hydrochloride (4.2 g, 13 mmol) and DIEA (7.5 g, 58 mmol) in ACN (42 mL) was added di-*tert*-butyl dicarbonate (4.7 g, 21 mmol) dropwise at 0 °C under N₂. After stirring for 1 hr at rt, the mixture was purified by reverse phase column chromatography with the following conditions (Column: WelFlash TM C18-I, 20-40 µm, 330 g; Eluent A: Water; Eluent B: ACN; Gradient: 25% - 45% B in 25 min; Flow rate: 60 mL/min; Detector: 220/254 nm) to afford Intermediate **J** (3.3 g). LCMS (ESI, m/z): [M+H-56]⁺ 332.2.

Intermediate K

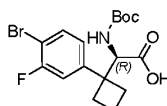
1-(4-bromo-3-fluorophenyl)cyclobutane-1-carbaldehyde (K)



[0216] Following conditions analogous to synthesis of Intermediate **A-2**, Intermediate **K** was prepared from 2-(4-bromo-3-fluorophenyl)acetonitrile. ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 7.56-7.52 (m, 1H), 6.94-6.91 (m, 1H), 6.83-6.80 (m, 1H), 2.76-2.70 (m, 2H), 2.41-2.34 (m, 2H), 2.10-1.90 (m, 2H).

Intermediate L

(R)-2-(1-(4-bromo-3-fluorophenyl)cyclobutyl)-2-((tert-butoxycarbonyl)amino)acetic acid (L)

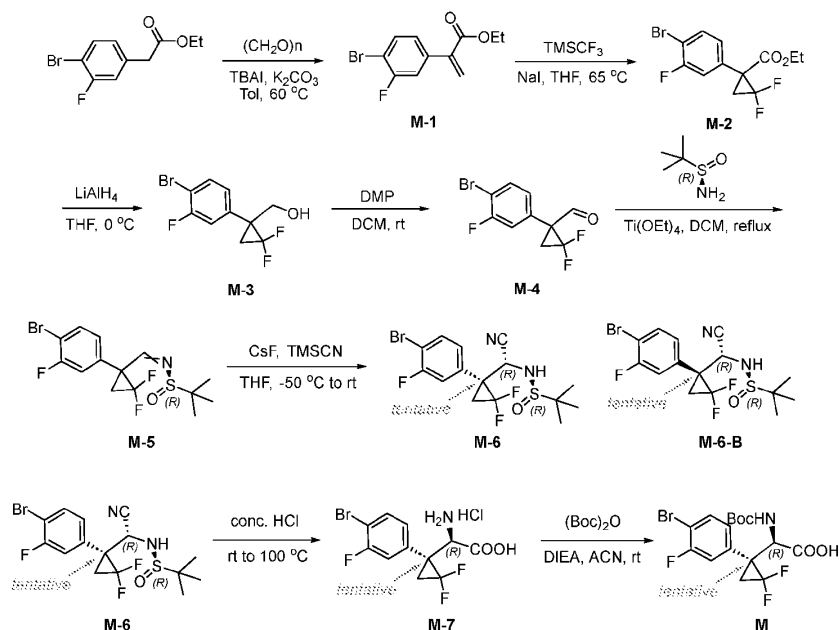


[0217] Following conditions analogous to the alternative synthesis of **B**, Intermediate **L** was synthesized from **K**. LCMS (ESI, m/z): [M+H]⁺ 402.1.

Intermediate M

(R)-2-((R)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)-2-((tert-butoxycarbonyl)amino)acetic acid (M)

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**Step 1: Ethyl 2-(4-bromo-3-fluorophenyl)acrylate (M-1)**

[0218] A mixture of ethyl 2-(4-bromo-3-fluorophenyl)acetate (2.0 g, 7.7 mmol), paraformaldehyde (700 mg, 23.1 mmol), K_2CO_3 (3.2 g, 23 mmol) and TBAI (129 mg, 0.35 mmol) in toluene (25 mL) was stirred at 60°C for 1 hr. The resulting mixture was filtered, and the filter cake washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford ethyl 2-(4-bromo-3-fluorophenyl)acrylate (1.1 g). GCMS m/z 271.9 [M].

Step 2: Ethyl 1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carboxylate (M-2)

[0219] A mixture of ethyl 2-(4-bromo-3-fluorophenyl)acrylate (500 mg, 1.8 mmol) and NaI (82 mg, 0.55 mmol) in THF (5 mL) was stirred at 65°C under N_2 for 10 min. TMSCF_3 (781 mg, 5.5 mmol) was added dropwise. After stirring at 65°C for another 8 hrs, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (99:1), to afford ethyl 1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carboxylate (200 mg). GCMS m/z 322.1 [M].

Step 3: (1-(4-Bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methanol (M-3)

[0220] To a mixture of ethyl 1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carboxylate (200 mg, 0.62 mmol) in THF (2 mL) was added LiAlH_4 (2 M in THF, 1.86 mmol, 0.93 mL) dropwise at 0°C under N_2 . After stirring for 2 hrs, the mixture was

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quenched with water and aqueous NaOH (15% solution), diluted with EtOAc and treated with MgSO₄. The mixture was filtered and the filtrate concentrated under reduced pressure to afford (1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methanol (170 mg). GCMS m/z 279.9 [M].

Step 4: 1-(4-Bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carbaldehyde (M-4)

[0221] A mixture of (1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methanol (200 mg, 0.71 mmol) and DMP (513 mg, 1.2 mmol) in DCM (10 mL) was stirred at rt for 3 hrs. The mixture was filtered, and the filtrate concentrated under reduced pressure to afford 1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carbaldehyde (130 mg). GCMS m/z 278.0 [M].

Step 5: (R)-N-((1-(4-Bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methylene)-2-methylpropane-2-sulfinamide (M-5)

[0222] A mixture of 1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropane-1-carbaldehyde (9 g, 32 mmol) and (R)-2-methylpropane-2-sulfinamide (4.3 g, 36 mmol) in DCM (90 mL) was added Ti(OEt)₄ (29.4 g, 0.13 mol) dropwise at rt under N₂. After stirring at reflux for 1 hr, the mixture was treated with water, filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (8:1), to afford (R)-N-((1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methylene)-2-methylpropane-2-sulfinamide (7.6 g). LCMS (ESI, m/z): [M+H]⁺ 382.4.

Step 6: (R)-N-((R)-((R)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (M-6) and (R)-N-((R)-((S)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)(cyano)methyl)-2-methylpropane-2-sulfinamide (M-6-B)

[0223] A mixture of (R)-N-((1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)methylene)-2-methylpropane-2-sulfinamide (1.8 g, 4.7 mmol) and CsF (0.95 g, 6.3 mmol) in THF (20 mL) was added TMSCN (0.63 g, 6.12 mmol) dropwise at -50 °C. After stirring at rt for 2 hrs, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford the product mixture. The diastereomeric mixture was separated by prep-Achiral-SFC (Column: DAICEL DCpak P4VP 3*25 cm, 5µm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (1% 2M NH₃-MeOH); Flow rate: 65 mL/min; Gradient (B%): isocratic 28% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm) to give Peak

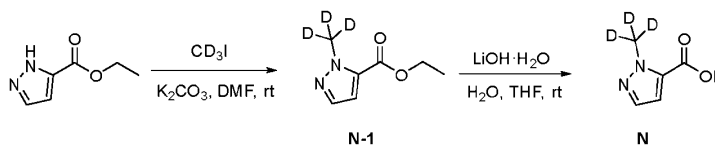
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1 as one pair of diastereomers and Peak 2 as the second pair of diastereomers. Peak 2 was further separated by prep-Chiral-HPLC (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μ m; Mobile Phase A: Hex (0.5% 2M NH_3 -MeOH), Mobile Phase B: MeOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient (B%): isocratic 20% B; Wave Length: 254/220nm) to afford Peak 1, which was tentatively assigned as (*R*)-*N*-((*R*)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)-(cyano)methyl-2-methylpropane-2-sulfinamide, and Peak 2, which was tentatively assigned as (*R*)-*N*-((*R*)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)(cyano)-methyl-2-methylpropane-2-sulfinamide. LCMS (ESI, *m/z*): $[\text{M}+\text{H}]^+$ 411.2.

[0224] Following conditions analogous to the alternative synthesis of Intermediate **B**, Intermediate **M** was synthesized from Intermediate **M-6**, via steps 7 and 8. LCMS (ESI, *m/z*): $[\text{M}-\text{H}]^-$ 424.0.

Intermediate N

1-(methyl-*d*₃)-1*H*-pyrazole-5-carboxylic acid (**N**)



Step 1: Ethyl 1-(methyl-*d*₃)-1*H*-pyrazole-5-carboxylate (**N-1**)

[0225] A mixture of ethyl 1*H*-pyrazole-5-carboxylate (8.0 g, 57 mmol), iodomethane-*d*₃ (9.9 g, 69 mmol) and K_2CO_3 (15.8 g, 114 mmol) in DMF (80 mL) was stirred for 4 hrs at rt under N_2 . The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford ethyl 1-(methyl-*d*₃)-1*H*-pyrazole-5-carboxylate (4 g). LCMS (ESI, *m/z*): $[\text{M}+\text{H}]^+$ 158.1.

Step 2: 1-(Methyl-*d*₃)-1*H*-pyrazole-5-carboxylic acid (**N**)

[0226] A mixture of ethyl 1-(methyl-*d*₃)-1*H*-pyrazole-5-carboxylate (400 mg, 2.5 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (320 mg, 7.6 mmol) in THF (4 mL) and H_2O (4 mL) was stirred for 2 hrs at rt. After removal of most THF under reduced pressure, the residue was acidified to pH 2-3 with HCl solution (3 M in water) and extracted with EtOAc. The combined organic layers were

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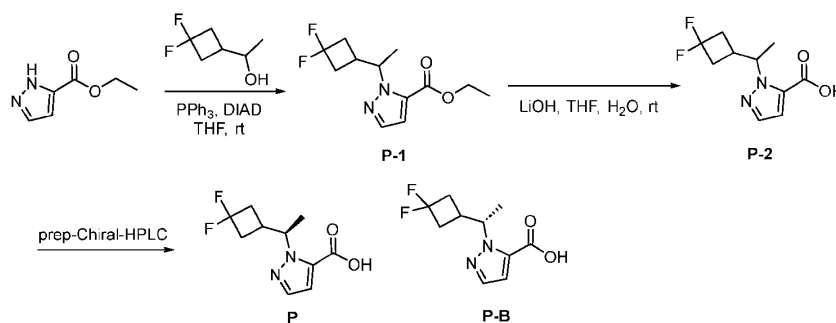
washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford Intermediate **N** (300 mg). LCMS (ESI, m/z): [M+H]⁺ 130.1.

[0227] Following conditions analogous to synthesis of **N**, Intermediate **O** in the table below was synthesized from ethyl 1*H*-pyrazole-5-carboxylate.

Int. #	Structure	Name	LCMS (ESI, m/z)
O		1-(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxylic acid	[M+H] ⁺ 211.1

Intermediate **P**

(*R*)-1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylic acid (**P**)



Step 1: Ethyl 1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylate (**P-1**)

[0228] A mixture of 1-(3,3-difluorocyclobutyl)ethan-1-ol (700 mg, 5.1 mmol), PPh₃ (4.0 g, 15 mmol) and ethyl 1*H*-pyrazole-5-carboxylate (793 mg, 5.7 mmol) in THF (2 mL) was added DIAD (3.1 g, 15 mmol) dropwise at rt under N₂. After stirring for 4 hrs, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (12:1), to afford ethyl 1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylate (780 mg). LCMS (ESI, m/z): [M+H]⁺ 259.1.

Step 2: 1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylic acid (**P-2**)

[0229] A mixture of ethyl 1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylate (780 mg, 3.0 mmol) and LiOH (362 mg, 15.1 mmol) in THF (7 mL) and H₂O (7 mL) was stirred at rt for 4 hrs. The mixture was acidified to pH 4-5 with aqueous HCl (1M) and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 1-(1-(3,3-difluorocyclobutyl)ethyl)-1*H*-pyrazole-5-carboxylic acid. LCMS (ESI, m/z): [M+H]⁺ 231.1.

Step 3: (R)-1-(1-(3,3-difluorocyclobutyl)ethyl)-1H-pyrazole-5-carboxylic acid (P)

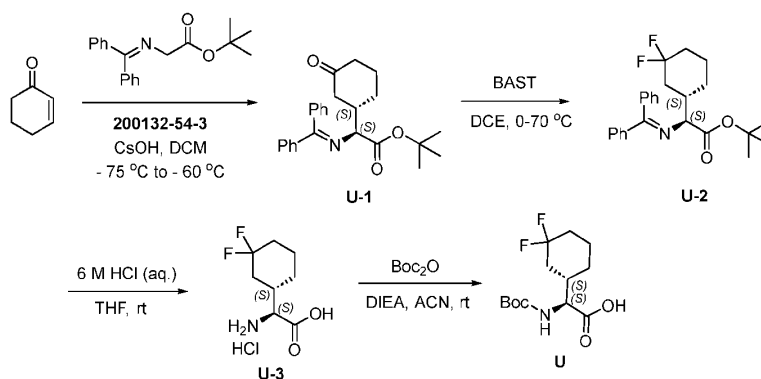
[0230] Intermediate **P-2** was resolved by prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SZ 3*25 cm, 5um; Mobile Phase A: CO₂, Mobile Phase B: MeOH (0.1%-DEA); Flow rate: 75 mL/min; Gradient (B%): isocratic 10% B; Temperature (°C) 35; Back Pressure(bar): 100; Wave Length: 220 nm) to afford peak 1 arbitrarily assigned as Intermediate **P** and peak 2 arbitrarily assigned as **P-B**. LCMS (ESI, m/z): [M+H]⁺ 231.1

[0231] Following conditions analogous to synthesis of **P-2**, Intermediates in the table below were synthesized from ethyl 1H-pyrazole-5-carboxylate.

Intermediates	Name LCMS (ESI, m/z)	Intermediates	Name LCMS (ESI, m/z)
	1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1H-pyrazole-5-carboxylic acid [M+H] ⁺ 211.1		1-((3,3-difluorocyclobutyl)methyl)-1H-pyrazole-5-carboxylic acid [M+H] ⁺ 217.0
	1-(cyclobutylmethyl)-1H-pyrazole-5-carboxylic acid [M+H] ⁺ 181.2		(R)-1-((tetrahydrofuran-2-yl)methyl)-1H-pyrazole-5-carboxylic acid [M+H] ⁺ 197.1

Intermediate U

(S)-2-((tert-butoxycarbonyl)amino)-2-((S)-3,3-difluorocyclohexyl)acetic acid (U)



Step 1: tert-Butyl (S)-2-((diphenylmethylene)amino)-2-((S)-3-oxocyclohexyl)acetate (U-1)

[0232] Reference: Chinchilla, R.; *et al* *ARKIVOC* 2005, 6, 222-232.

[0233] To a stirred mixture of *tert*-butyl 2-((diphenylmethylene)amino)acetate (5.0 g, 17 mmol), cesium hydroxide (28.4 g, 169 mmol) and (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(allyloxy)(quinolin-4-yl)methyl)-1-(anthracen-9-ylmethyl)-5-vinylquinuclidin-1-ium bromide (CAS: 200132-54-3, 1.1 g, 1.7 mmol) in DCM (70 mL) was added cyclohex-2-en-1-one (5.2 g, 54 mmol) dropwise over 15 min at -78 °C under N₂. After stirring for 30 mins at -78 °C and 6 hrs at -60 °C, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford *tert*-butyl (*S*)-2-((diphenylmethylene)amino)-2-((*S*)-3-oxocyclohexyl)acetate (3.5 g). LCMS (ESI, *m/z*): [M+H]⁺ 392.3.

Step 2: *tert*-Butyl (*S*)-2-((*S*)-3,3-difluorocyclohexyl)-2-((diphenylmethylene)amino)acetate (U-2)

[0234] A solution of *tert*-butyl (*S*)-2-((diphenylmethylene)amino)-2-((*S*)-3-oxocyclohexyl)acetate (2.2 g, 5.6 mmol) and BAST (11 mL, 56 mmol) in DCE (20 mL) was stirred for 30 min at 0 °C under N₂, then at 70 °C for 16 hrs. The mixture was quenched with saturated NaHCO₃ solution at 0 °C and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase: ACN in water (10 mmol/L NH₄HCO₃); flow rate: 60 mL/min, 0% to 100% gradient in 40 min) to afford *tert*-Butyl (*S*)-2-((*S*)-3,3-difluorocyclohexyl)-2-((diphenylmethylene)amino)acetate (1.4 g). LCMS (ESI, *m/z*): [M+H]⁺ 414.2.

Step 3: (*S*)-2-amino-2-((*S*)-3,3-difluorocyclohexyl)acetic acid hydrochloride (U-3)

[0235] A solution of *tert*-butyl (*S*)-2-((*S*)-3,3-difluorocyclohexyl)-2-((diphenylmethylene)amino)-acetate (1.1 g, 2.7 mmol) in THF (2 mL) and aqueous HCl (6 M, 20 mL) was stirred at rt for 20 hrs and concentrated under reduced pressure. The residue was washed by DCM to afford (*S*)-2-Amino-2-((*S*)-3,3-difluorocyclohexyl)acetic acid HCl salt (0.8 g). LCMS (ESI, *m/z*): [M+H]⁺ 194.1.

Step 4: (*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-((*S*)-3,3-difluorocyclohexyl)acetic acid (U)

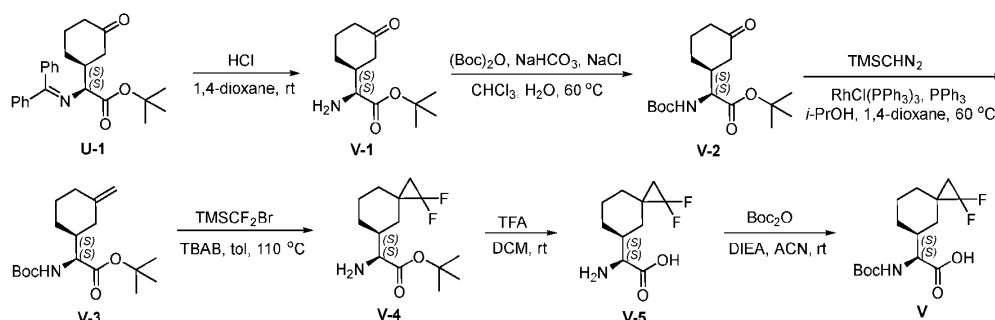
[0236] To a solution of (*S*)-2-amino-2-((*S*)-3,3-difluorocyclohexyl)acetic acid hydrochloride (0.8 g, 3.5 mmol) and DIEA (22 mL, 12 mmol) in ACN (10 mL) was added Boc₂O (1.4 g, 6.2 mmol) dropwise at 0 °C. After stirring at rt for 1 hr, the mixture was purified by reversed-

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phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase, ACN in deionized water; flow rate: 60 mL/min, 0% to 30% gradient in 40 min) to afford Intermediate U (0.75 g). LCMS (ESI, m/z): [M+H-56]⁺ 237.9.

Intermediate V

(2S)-2-((tert-butoxycarbonyl)amino)-2-((5S)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (V)



Step 1: *tert*-Butyl (S)-2-amino-2-((S)-3-oxocyclohexyl)acetate (V-1)

[0237] A solution of *tert*-butyl (S)-2-((diphenylmethylene)amino)-2-((S)-3-oxocyclohexyl)acetate (9.0 g, 23 mmol) in THF (90 mL) and aqueous HCl (4 M, 90 mL) was stirred at rt for 2 hrs. After completion, the mixture was extracted with n-heptane to remove impurities. The aqueous layer was neutralized to pH = 6 by saturated NaHCO₃ solution and concentrated under reduced pressure to afford *tert*-butyl (S)-2-amino-2-((S)-3-oxocyclohexyl)acetate. LCMS (ESI, m/z): [M+H]⁺ 228.1.

Step 2: *tert*-Butyl (S)-2-((tert-butoxycarbonyl)amino)-2-((S)-3-oxocyclohexyl)acetate (V-2)

[0238] A solution of *tert*-butyl (S)-2-amino-2-((S)-3-oxocyclohexyl)acetate (10 g, 44 mmol), (Boc)₂O (22.1 g, 100 mmol), NaHCO₃ (18.5 g, 220 mmol), NaCl (25.7 g, 440 mmol) in CHCl₃ was stirred at 60 °C for 5 hrs. After completion, the mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1 to 10:3), to afford *tert*-butyl (S)-2-((tert-butoxycarbonyl)amino)-2-((S)-3-oxocyclohexyl)acetate (1 g). LCMS (ESI, m/z): [M+H-56]⁺ 216.1.

Step 3: *tert*-Butyl (S)-2-((tert-butoxycarbonyl)amino)-2-((S)-3-methylenecyclohexyl)acetate (V-3)

[0239] To a mixture of *tert*-butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-((*S*)-3-oxocyclohexyl)acetate (1.0 g, 3.1 mmol), RhCl(PPh₃)₃ (10 mg, 0.01 mmol) and PPh₃ (880 mg, 3.4 mmol) in 1,4-dioxane (20 mL) and isopropanol (3.5 mL) was added TMSCHN₂ (2 M in hexane, 3.7 mL, 7.4 mmol) dropwise at 60 °C under N₂. After stirring at 60 °C for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford *tert*-butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-((*S*)-3-methylenecyclohexyl)acetate (550 mg). LCMS (ESI, m/z): [M+H-56-56]⁺ 214.1.

Step 4: *tert*-Butyl (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (**V-4**)

[0240] A solution of *tert*-butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-2-((*S*)-3-methylenecyclohexyl)acetate (500 mg, 1.54 mmol), (bromodifluoromethyl)trimethylsilane (1.18 g, 5.82 mmol) and TBAB (19 mg, 0.058 mmol) in toluene (6 mL) was stirred at 110 °C for 0.5 hr under N₂. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase: MeCN in water (0.05% NH₄HCO₃), 60% to 80% gradient in 30 min) to afford *tert*-butyl (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (220 mg). LCMS (ESI, m/z): [M+H]⁺ 275.9.

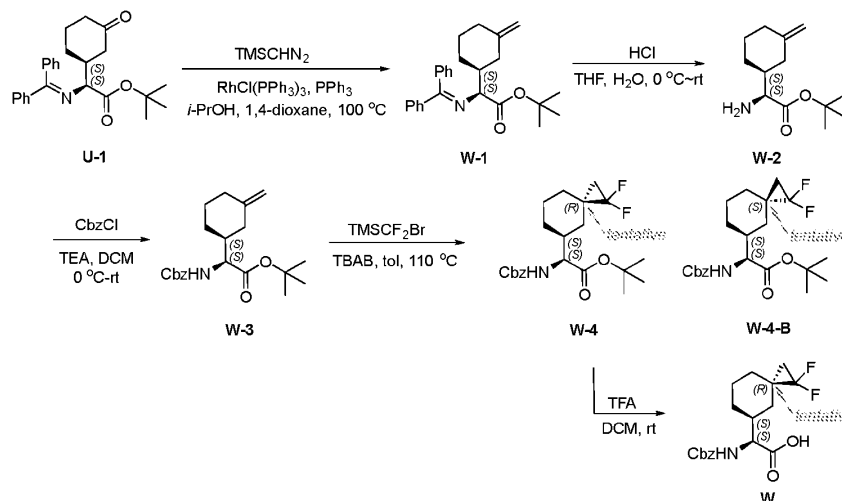
Step 5: (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (**V-5**)

[0241] A solution of *tert*-butyl (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (210 mg, 0.763 mmol) and TFA (0.5 mL) in DCM (2 mL) was stirred at rt for 2 days. The mixture was concentrated under reduced pressure to afford (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid. LCMS (ESI, m/z): [M+H]⁺ 220.1.

Step 6: (2*S*)-2-((*tert*-butoxycarbonyl)amino)-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (**V**)

[0242] A solution of (2*S*)-2-amino-2-((5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (165 mg, 0.75 mmol), (Boc)₂O (254 mg, 1.16 mmol) and DIEA (251 mg, 1.94 mmol) in ACN (0.5 mL) was stirred at rt for 6 hrs. The mixture was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel, 48 g; mobile phase: MeCN in water (0.05% NH₄HCO₃), 10% to 25% gradient in 10 min) to afford Intermediate **V** (40 mg). LCMS (ESI, m/z): [M+H]⁺ 319.8.

Intermediate W

(S)-2-(((benzyloxy)carbonyl)amino)-2-((3R,5S)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (W)Step 1: *tert*-Butyl (S)-2-((diphenylmethylene)amino)-2-((S)-3-methylenecyclohexyl)acetate (W-1)

[0243] Following conditions analogous to synthesis of **V-3**, Intermediate **W-1** was synthesized from **U-1**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 390.3.

Step 2: *tert*-Butyl (S)-2-amino-2-((S)-3-methylenecyclohexyl)acetate (W-2)

[0244] Following conditions analogous to synthesis of **V-1**, Intermediate **W-2** was synthesized from **W-1**. LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 226.1.

Step 3: *tert*-Butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((S)-3-methylenecyclohexyl)acetate (W-3)

[0245] To a stirred solution of *tert*-butyl (S)-2-amino-2-((S)-3-methylenecyclohexyl)acetate (1.0 g, 4.4 mmol) and TEA (2.0 g, 19.5 mmol) in DCM (0.5 mL) was added CbzCl (1.1 g, 6.5 mmol) dropwise at 0°C . After stirring at rt for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse-phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase: MeCN in water (0.05% NH_4HCO_3), 40% to 80% gradient in 60 min) to afford *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((S)-3-methylenecyclohexyl)acetate (1.5 g). LCMS (ESI, m/z): $[\text{M}+\text{H}-56]^+$ 304.0.

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Step 4: *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (W-4) and *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((3*S*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (W-4-B)

[0246] The mixture of *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((S)-3-methylenecyclohexyl)acetate (1.5 g, 4.2 mmol), (bromodifluoromethyl)trimethylsilane (2.5 g, 12.3 mmol) and TBAB (40 mg, 0.12 mmol) in toluene (5 mL) was stirred at 110 °C for 1 hr under N₂. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase: MeCN in water (0.05% NH₄HCO₃), 50% to 70% gradient in 30 min) to afford a diastereomeric mixture. The mixture was separated by SFC with the following conditions (Column: CHIRALPAK IG 3*25 cm, 5 µm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (1%-2M-NH₃-MeOH); Flow rate: 90 mL/min; Gradient (B%): isocratic 12% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford Peak 1, which was tentatively assigned as *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((3*S*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (W-4-B), and Peak 2, which was tentatively assigned as *tert*-butyl (S)-2-(((benzyloxy)carbonyl)amino)-2-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetate (W-4). LCMS (ESI, m/z): [M+H-56]⁺ 354.1.

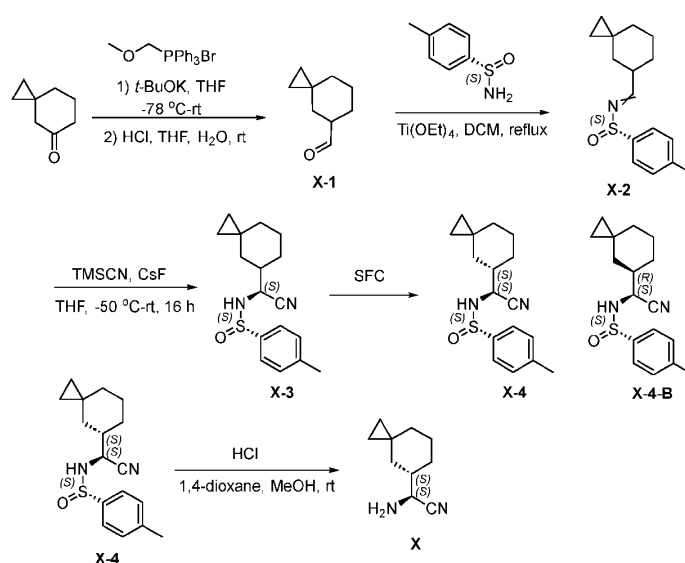
Step 5: (S)-2-(((benzyloxy)carbonyl)amino)-2-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)acetic acid (W)

[0247] Following conditions analogous to synthesis of V-5, Intermediate W was synthesized from W-4. LCMS (ESI, m/z): [M+H]⁺ 354.1.

Intermediate X

(S)-2-amino-2-((S)-spiro[2.5]octan-5-yl)acetonitrile (X)

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Step 1: Spiro[2.5]octane-5-carbaldehyde (X-1)

[0248] A solution of bromo(methoxymethyl)triphenyl-1⁵-phosphane (79 g, 204 mmol) in THF (800 mL) was added *t*-BuOK (1 M in THF, 230 mL, 230 mmol) dropwise at -78 °C under N₂. After stirring at -78 °C for 2 hrs, spiro[2.5]octan-5-one (22 g, 177 mmol) was added dropwise. After stirring for 16 hrs at rt, aqueous HCl (6 M, 100 mL) was added. The mixture was stirred for 2 h, treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford spiro[2.5]octane-5-carbaldehyde.

Step 2: (S)-4-methyl-N-(spiro[2.5]octan-5-ylmethylene)benzenesulfinamide (X-2)

[0249] A mixture of spiro[2.5]octane-5-carbaldehyde (20 g, 145 mmol), (S)-4-methylbenzenesulfinamide (22.5 g, 145 mmol) and Ti(OEt)₄ (99.2 g, 435 mol) in DCM (200 mL) was stirred at reflux for 4 hrs under N₂. The mixture was treated with water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography, eluting with PE/EtOAc (5:1), to afford (S)-4-methyl-N-(spiro[2.5]octan-5-ylmethylene)benzenesulfinamide (20 g). LCMS (ESI, m/z): [M+H]⁺ 276.1.

Step 3: (S)-N-((1S)-cyano(spиро[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-3)

[0250] To a solution of (S)-4-methyl-N-(spiro[2.5]octan-5-ylmethylene)benzenesulfinamide (20 g, 73 mmol), CsF (15.2 g, 100 mmol) in THF (10 mL) was added TMSCN (23 g, 232

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mmol) at -50 °C under N₂. After stirring at rt for 16 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography, eluting with PE/EtOAc (3:1), to afford (S)-N-((1S)-cyano(spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (20 g). LCMS (ESI, m/z): [M+H]⁺ 303.1.

Step 4: (S)-N-((S)-cyano((S)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4) and (S)-N-((S)-cyano((R)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4-B)

[0251] (S)-N-((1S)-cyano(spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide was separated by SFC with the following conditions (Column: CHIRALPAK IG 5*25 cm, 5μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (0.3% 7M NH₃-MEOH); Flow rate: 180 mL/min; Gradient (B%): isocratic 36% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford peak 1 as a mixture of (S)-N-((S)-cyano((S)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4) and (S)-N-((S)-cyano((R)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4-B), and peak 2 as a mixture of two minor isomers. Peak 1 was further separated by SFC with the following conditions (Column: CHIRAL ART Cellulose-SZ 3*25 cm, 5μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH(0.3% 7M NH₃-MEOH); Flow rate: 85 mL/min; Gradient (B%): isocratic 14% B; Column Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford first peak as (S)-N-((S)-cyano((S)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4) and second peak as (S)-N-((S)-cyano((R)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (X-4-B). LCMS (ESI, m/z): [M+H]⁺ 303.1.

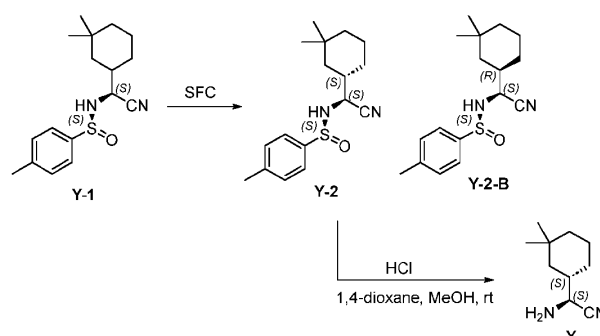
Step 5: (S)-2-amino-2-((S)-spiro[2.5]octan-5-yl)acetonitrile (X)

[0252] A solution of (S)-N-((S)-cyano((S)-spiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (1 g, 3.31 mmol) and HCl (4 M in 1,4-dioxane, 1 mL) in MeOH (1 mL) was stirred for 2 hrs at rt. The mixture was concentrated under reduced pressure, treated with water and washed with Et₂O to remove impurities. The aqueous layer was adjusted to pH 8-9 with saturated NaHCO₃ and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford Intermediate X (520 mg). LCMS (ESI, m/z): [M+H]⁺ 165.1.

Intermediate Y

(S)-2-amino-2-((S)-3,3-dimethylcyclohexyl)acetonitrile (Y)

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[0253] Following conditions analogous to synthesis of **X-3**, Intermediate **Y-1** was synthesized from the commercially available ketone.

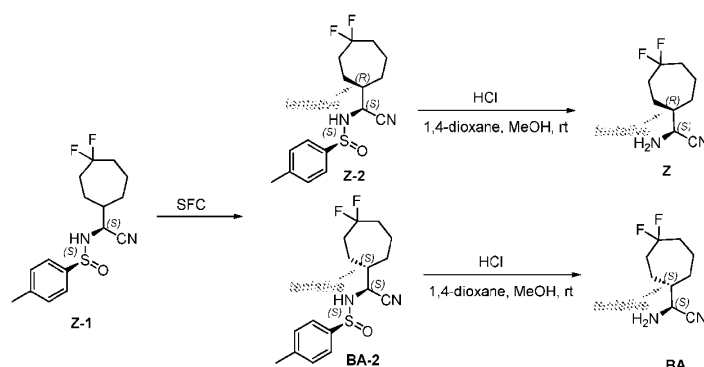
[0254] Intermediate **Y-1** was separated by SFC with the following conditions (System: Waters SFC 150, Column name: DAICEL CHIRALPAK®OD-10, Column size: 25*250mm 10 µm, Mobile Phase A: Supercritical CO₂, Mobile Phase B: MeOH (0.05% NH₃·MeOH), A:B= 90:10, Wavelength: 214 nm/254 nm, Flow:60 mL/min, Column temp: RT) to afford peak 1 as a mixture of (*S*)-*N*-((*S*)-cyano(*S*)-3,3-dimethylcyclohexyl)methyl)-4-methylbenzenesulfonamide (**Y-2**) and one minor isomer, and peak 2 as a mixture of (*S*)-*N*-((*S*)-cyano(*R*)-3,3-dimethylcyclohexyl)methyl)-4-methylbenzenesulfonamide (**Y-2-B**) and one other minor isomer. Peak 1 was further separated by SFC with the following conditions (System: Waters SFC 150, Column name: DAICEL CHIRALPAK®AS-10, Column size: 25*250mm 10 µm, Mobile Phase A: Supercritical CO₂, Mobile Phase B: MeOH (0.05% NH₃ · MeOH), A:B= 80:20, Wavelength:214 nm/254 nm, Flow:60 mL/min, Column temp: RT) to afford the major peak as (*S*)-*N*-((*S*)-cyano(*S*)-3,3-dimethylcyclohexyl)methyl)-4-methylbenzenesulfonamide (**Y-2**). LCMS (ESI, m/z): [M+H]⁺ 305.2.

[0255] Following conditions analogous to synthesis of **X**, Intermediate **Y** was synthesized from **Y-2**. LCMS (ESI, m/z): [M+H]⁺ 167.1.

Intermediates Z and BA

(*S*)-2-amino-2-((*R*)-4,4-difluorocycloheptyl)acetonitrile hydrochloride (**Z**) and (*S*)-2-amino-2-((*S*)-4,4-difluorocycloheptyl)acetonitrile hydrochloride (**BA**)

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[0256] Following conditions analogous to synthesis of Intermediate **X-3**, Intermediate **Z-1** was synthesized from the commercially available ketone.

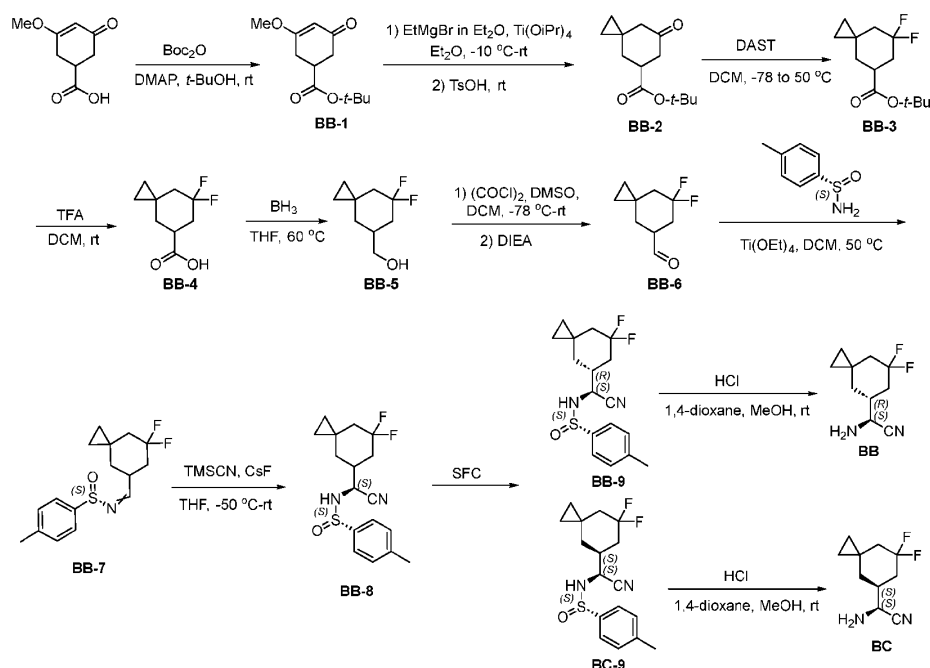
[0257] Intermediate **Z-1** was purified by SFC with the following conditions (Column: CHIRAL ART Amylose-C NEO 5*25 cm, 5um; Mobile Phase A: CO₂, Mobile Phase B: MeOH(1%-2M-NH₃-MeOH); Flow rate: 140 mL/min; Gradient: isocratic 28% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm) to give the first major peak, which was tentatively assigned as (S)-N-((S)-cyano((R)-4,4-difluorocycloheptyl)methyl)-4-methylbenzenesulfonamide (**Z-2**), and the second major peak, which was tentatively assigned as (S)-N-((S)-cyano((S)-4,4-difluorocycloheptyl)methyl)-4-methylbenzenesulfonamide (**BA-2**). LCMS (ESI, m/z): [M+H]⁺ 327.1.

[0258] Following conditions analogous to synthesis of **X**, Intermediate **Z** was synthesized from **Z-2** and intermediate **BA** from **BA-2**. LCMS (ESI, m/z): [M+H]⁺ 189.1.

Intermediates BB and BC

(S)-2-amino-2-((R)-7,7-difluorospiro[2.5]octan-5-yl)acetonitrile (**BB**) and (S)-2-amino-2-((S)-7,7-difluorospiro[2.5]octan-5-yl)acetonitrile (**BC**)

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Step 1: *tert*-Butyl 3-methoxy-5-oxocyclohex-3-ene-1-carboxylate (**BB-1**)

[0259] To a stirred mixture of 3-methoxy-5-oxocyclohex-3-ene-1-carboxylic acid (12 g, 70.5 mmol) in *t*-BuOH (100 mL) at 0 °C under nitrogen were added DMAP (12 g, 98.3 mmol) and Boc₂O (46 g, 210 mmol) in portions. After stirring at rt for 16 hrs, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford *tert*-Butyl 3-methoxy-5-oxocyclohex-3-ene-1-carboxylate (16 g). LCMS (ESI, *m/z*): [M+H]⁺ 227.1

Step 2: *tert*-Butyl 7-oxospiro[2.5]octane-5-carboxylate (**BB-2**)

[0260] To a stirred mixture of *tert*-butyl 3-methoxy-5-oxocyclohex-3-ene-1-carboxylate (15 g, 66 mmol) in diethyl ether (375 mL) at -10 °C under N₂ was added titanium tetraisopropanolate (8.2 g, 29 mmol) in portions. After stirring for 10 mins, ethyl magnesium bromide (3 M in diethyl ether, 75 mL, 225 mmol) was added portion wise over 2 hrs at -10 °C. After stirring at rt for an additional 2 hrs, the mixture was quenched with saturated NH₄Cl solution. The resulting mixture was filtered and extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄ and filtered. The resulting filtrate was treated with TsOH (0.38 g, 2.2 mmol). After stirring at rt for 16 hrs, the mixture was washed with saturated NaHCO₃, dried over anhydrous Na₂SO₄, filtered and

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concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford *tert*-butyl 7-oxospiro[2.5]octane-5-carboxylate (2.5 g). ¹H NMR (400 MHz, CDCl₃) δ 2.89-2.79 (m, 1H), 2.63-2.50 (m, 3H), 2.13-2.04 (m, 1H), 1.82-1.76 (m, 1H), 1.51-1.47 (m, 1H), 1.44 (s, 9H), 0.55-0.48 (m, 1H), 0.45-0.33 (m, 3H).

Step 3: *tert*-Butyl 7,7-difluorospiro[2.5]octane-5-carboxylate (BB-3)

[0261] To a solution of *tert*-butyl 7-oxospiro[2.5]octane-5-carboxylate (2.5 g, 11.2 mmol) in DCM (30 mL) at -78 °C under N₂ was added DAST (14.4 g, 89.3 mmol) dropwise. After stirring at 50 °C for 16 hrs, the mixture was quenched with saturated NH₄Cl and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford *tert*-butyl 7,7-difluorospiro[2.5]octane-5-carboxylate (1.2 g). ¹H NMR (400 MHz, CDCl₃) δ 2.75-2.64 (m, 1H), 2.44-2.31 (m, 1H), 2.21-2.04 (m, 1H), 1.92-1.73 (m, 2H), 1.49-1.46 (m, 2H), 1.44 (s, 9H), 0.54-0.34 (m, 4H).

Step 4: 7,7-Difluorospiro[2.5]octane-5-carboxylic acid (BB-4)

[0262] Following conditions analogous to synthesis of V-5, Intermediate BB-4 was synthesized from BB-3.

Step 5: (7,7-difluorospiro[2.5]octan-5-yl)methanol (BB-5)

[0263] A mixture of 7,7-difluorospiro[2.5]octane-5-carboxylic acid (1 g, 4.2 mmol) in borane-tetrahydrofuran complex (1 M in THF, 10 mL) was stirred at 60 °C for 16 hrs. The mixture was quenched with MeOH (20 mL) at 0 °C and concentrated under reduced pressure to afford (7,7-difluorospiro[2.5]octan-5-yl)methanol.

Step 6: 7,7-Difluorospiro[2.5]octane-5-carbaldehyde (BB-6)

[0264] To solution of DMSO (333 mg, 4.3 mmol) in DCM (20 mL) at -78 °C under N₂ was added oxalyl chloride (533 mg, 4.2 mmol) dropwise. After stirring at -78 °C for 15 mins, a solution of (7,7-difluorospiro[2.5]octan-5-yl)methanol (600 mg, 3.4 mmol) in DCM (10 mL) was added dropwise over 5 mins. After stirring for additional 1 hr, Et₃N (861 mg, 8.5 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 mins, treated with KH₂PO₄ (20% in H₂O, 10 ml) and water (10 ml), and extracted with DCM. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 7,7-difluorospiro[2.5]octane-5-carbaldehyde.

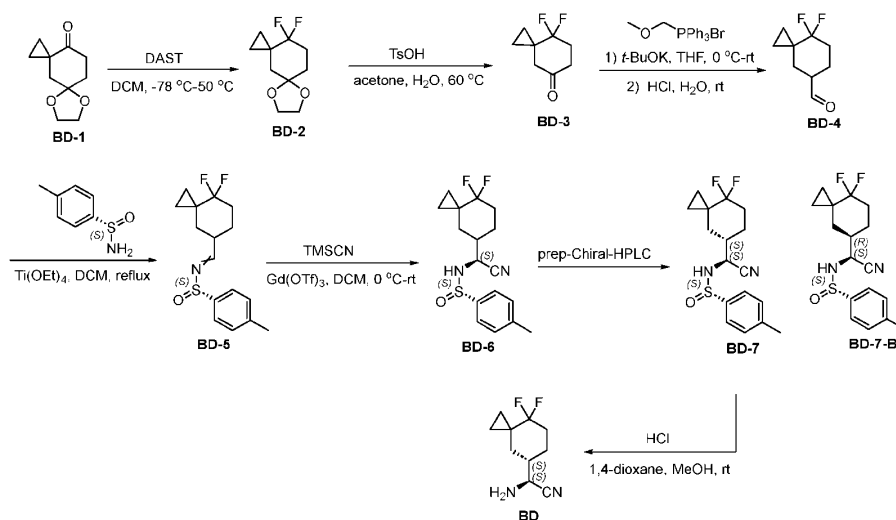
[0265] Following conditions analogous to synthesis of **X-3**, Intermediate **BB-8** was synthesized from **BB-6**.

[0266] Intermediate **BB-8** was separated by SFC with the following conditions (Column: CHIRALPAK IG 3*25 cm, 5μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (0.3% 7M NH₃-MeOH); Flow rate: 80 mL/min; Gradient: isocratic 14% B; Column Temperature(°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to give the first major peak as (*S*)-*N*-((*S*)-cyano((*R*)-7,7-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfonamide (**BB-9**) and the second major peak as (*S*)-*N*-((*S*)-cyano((*S*)-7,7-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfonamide (**BC-9**). LCMS (ESI, *m/z*): [M+H]⁺ 339.1.

[0267] Following conditions analogous to synthesis of **X**, Intermediate **BB** was synthesized from **BB-9** and Intermediate **BC** was synthesized from **BC-9**. LCMS (ESI, *m/z*): [M+H]⁺ 201.1.

Intermediate BD

(*S*)-2-Amino-2-((*S*)-8,8-difluorospiro[2.5]octan-5-yl)acetonitrile (**BD**)



Step 1: 12,12-difluoro-6,9-dioxadispiro[2.1.4⁵.3³]dodecane (**BD-2**)

[0268] Following conditions analogous to synthesis of **BB-3**, Intermediate **BD-2** was synthesized from **BD-1** (*Chemical Communications*, **1998**, 12, 1287 – 1288).

Step 2: 8,8-Difluorospiro[2.5]octan-5-one (**BD-3**)

[0269] A mixture of 12,12-difluoro-6,9-dioxadispiro[2.1.4⁵.3³]dodecane (1.3 g, 6.4 mmol) and TsOH (0.66 g, 3.8 mmol) in acetone (10 mL) and H₂O (3 mL) was stirred at 60 °C for 16

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hrs. The mixture was concentrated under reduced pressure, treated with water and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 8,8-difluorospiro[2.5]octan-5-one (700 mg).

[0270] Following conditions analogous to synthesis of **X-2**, Intermediate **BD-5** was synthesized from **BD-3**, via steps 3 and 4.

Step 5: (S)-N-((1S)-cyano(8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (BD-6)

[0271] To a mixture of (S)-N-((8,8-difluorospiro[2.5]octan-5-yl)methylene)-4-methylbenzenesulfinamide (240 mg, 0.77 mmol) and Gd(OTf)₃ (47 mg, 0.077 mmol) in DCM (2.4 mL) at 0 °C under N₂ was added TMSCN (153 mg, 1.5 mmol). After stirring at rt for 4 hrs. the mixture was treated with ice water and extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford (S)-N-((1S)-cyano(8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (150 mg). LCMS (ESI, m/z): [M+H]⁺ 339.1.

Step 6: (S)-N-((S)-cyano((S)-8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (BD-7) and (S)-N-((S)-cyano((R)-8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (BD-7-B)

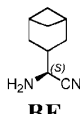
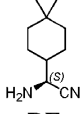
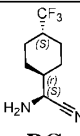
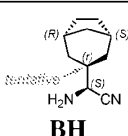
[0272] Intermediate **BD-6** was separated by prep-Chiral-HPLC with the following conditions (Column: Chiral ART Cellulose-SA, 2*25 cm, 5 µm; Mobile Phase A: Hex (0.5% 2M NH₃-MeOH), Mobile Phase B: EtOH: DCM=1: 1; Flow rate: 20 mL/min; Gradient (B%): isocratic 10% B; Wave Length: 254 nm/220 nm) to give the first major peak as (S)-N-((S)-cyano((S)-8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (**BD-7**) and the second major peak as (S)-N-((S)-cyano((R)-8,8-difluorospiro[2.5]octan-5-yl)methyl)-4-methylbenzenesulfinamide (**BD-7-B**). LCMS (ESI, m/z): [M+H]⁺ 339.1. **BD-7**: ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.53 (d, J = 8.4 Hz, 1H), 4.02-3.99 (m, 1H), 2.49 (s, 3H), 2.28-2.19 (m, 1H), 2.11-1.64 (m, 5H), 1.23-1.16 (m, 1H), 1.12-1.06 (m, 1H), 0.77-0.71 (m, 1H), 0.51-0.38 (m, 2H). **BD-7-B**: ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.54 (d, J = 8.0 Hz, 1H), 4.05-4.00 (m, 1H), 2.47 (s, 3H), 2.28-2.17 (m, 1H), 2.13-2.01 (m, 3H), 1.94-1.78 (m, 1H), 1.69-1.62 (m, 1H) 1.30-1.21 (m, 1H), 1.12-1.06 (m, 1H), 0.79-0.72 (m, 1H), 0.50-0.38 (m, 2H).

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Step 7: (S)-2-Amino-2-((S)-8,8-difluorospiro[2.5]octan-5-yl)acetonitrile (**BD**)

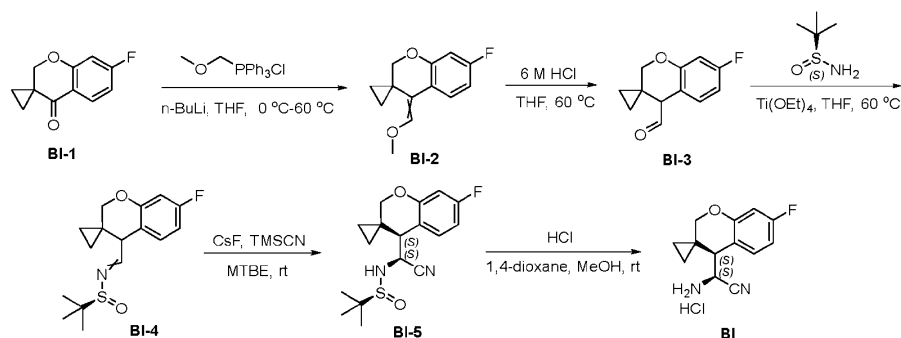
[0273] Following conditions analogous to synthesis of **X**, Intermediate **BD** was synthesized from **BD-7**. LCMS (ESI, m/z): [M+H]⁺ 201.1.

[0274] Following conditions analogous to synthesis of **X**, the intermediates in the table below were synthesized from corresponding ketones.

Intermediates	Name LCMS (ESI, m/z)	Intermediates	Name LCMS (ESI, m/z)
 BE	(S)-2-amino-2-(bicyclo[3.1.1]heptan-3-yl)acetonitrile [M+H] ⁺ 151.1	 BF	(S)-2-amino-2-(spiro[2.5]octan-6-yl)acetonitrile [M+H] ⁺ 165.2
 BG	(S)-2-amino-2-((1r,4S)-4-(trifluoromethyl)-cyclohexyl)acetonitrile [M+H] ⁺ 207.1	 BH	(S)-2-amino-2-((1R,3r,5S)-bicyclo[3.2.1]octan-3-yl)acetonitrile [M+H] ⁺ 165.1

Intermediate BI

(S)-2-amino-2-((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetonitrile (**BI**)



[0275] Intermediate **BI-1** was synthesized following “WO2022/007462, 2022, A1”.

Step 1: 7-fluoro-4-(methoxymethylene)spiro[chromane-3,1'-cyclopropane] (**BI-2**)

[0276] To a mixture of (methoxymethyl)triphenylphosphonium chloride (58.1 g, 169 mmol) in THF (125 mL) at 0 °C under N₂ was added *n*-BuLi (2.5 M in *n*-hexane, 68 mL, 169 mmol) dropwise. After stirring for 1 hr, 7-fluorospiro[chromane-3,1'-cyclopropan]-4-one (25.0 g, 130 mmol) in THF (125 mL) was added dropwise. The mixture was stirred at 60 °C for 2 hrs, treated with saturated NH₄Cl and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced

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pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (10:1), to afford 7-fluoro-4-(methoxymethylene)spiro[chromane-3,1'-cyclopropane] (30.0 g). GCMS m/z 220.1 for [M].

Step 2: 7-Fluorospiro[chromane-3,1'-cyclopropane]-4-carbaldehyde (BI-3)

[0277] To a mixture of 7-fluoro-4-(methoxymethylene)spiro[chromane-3,1'-cyclopropane] (25 g, 114 mmol) in THF (125 mL) at 0 °C was added HCl (6 M in water, 125 mL). After stirring at 60 °C for 3 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated NaHCO₃ and saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 7-fluorospiro[chromane-3,1'-cyclopropane]-4-carbaldehyde. GCMS m/z = 206.0 for [M].

Step 3: (S)-N-((7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methylene)-2-methylpropane-2-sulfinamide (BI-4)

[0278] A mixture of 7-fluorospiro[chromane-3,1'-cyclopropane]-4-carbaldehyde (25.0 g, 121 mmol), (S)-2-methylpropane-2-sulfinamide (14.7 g, 121 mmol) and Ti(OEt)₄ (51 mL, 242 mmol) in THF (250 mL) was stirred for 1 hr at 60 °C under N₂. The mixture was treated with water/EtOAc, filtered and the filtrate extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (3:1), to afford (S)-N-((7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methylene)-2-methylpropane-2-sulfinamide (18.0 g). LCMS (ESI, m/z): [M+H]⁺ 310.1.

Step 4: (S)-N-((S)-Cyano((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-2-methylpropane-2-sulfinamide (BI-5)

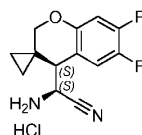
[0279] To a mixture of (S)-N-((7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methylene)-2-methylpropane-2-sulfinamide (17.0 g, 55 mmol) and CsF (16.7 g, 110 mmol) in MTBE (85 mL) at 0 °C under N₂ was added TMSCN (14 mL, 110 mmol). After stirring for 16 hrs at rt, the precipitates were collected by filtration and washed with MTBE. The solid was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by trituration with MTBE to afford chiral pure (S)-N-((S)-cyano((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-2-methylpropane-2-sulfinamide (6.0 g). LCMS (ESI, m/z): [M+H]⁺ 337.0.

Step 5: (S)-2-Amino-2-((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetonitrile hydrochloride (BI)

[0280] A mixture of (S)-N-((S)-cyano((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-2-methylpropane-2-sulfinamide (485 mg, 1.43 mmol) and HCl (4.0 M in 1,4-dioxane, 1.6 mL) in methanol (4.8 mL) was stirred for 1 hr at rt. The mixture was concentrated under reduced pressure. The residue was purified by trituration with MTBE to afford Intermediate **BI** (400 mg) as HCl salt. LCMS (ESI, m/z): [M+H]⁺ 233.1.

Intermediate BJ

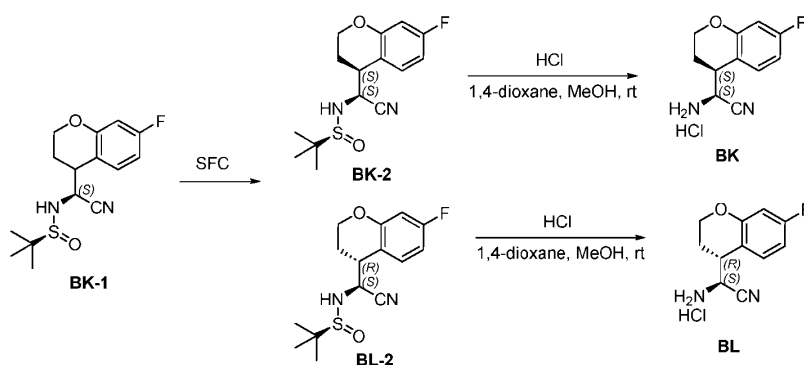
(S)-2-amino-2-((S)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetonitrile (BJ)



[0281] Intermediate **BJ** was synthesized as HCl salt, following conditions analogous to synthesis of Intermediate **BI**. LCMS (ESI, m/z): [M+H]⁺ 251.0.

Intermediates BK and BL

(S)-2-amino-2-((S)-7-fluorochroman-4-yl)acetonitrile hydrochloride (BK) and (S)-2-amino-2-((R)-7-fluorochroman-4-yl)acetonitrile hydrochloride (BL)



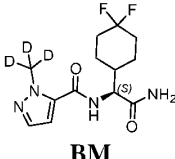
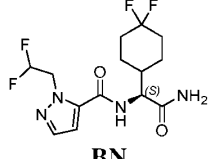
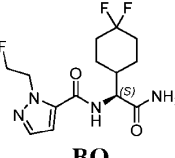
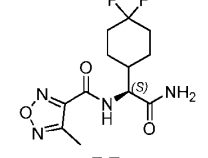
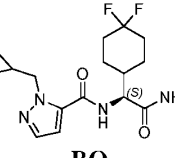
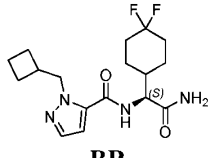
[0282] Following conditions analogous to synthesis of **X-3**, Intermediate **BK-1** was synthesized from the commercially available ketone.

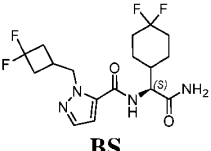
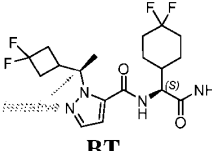
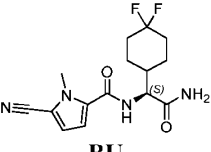
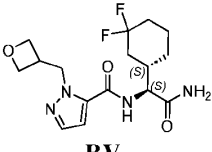
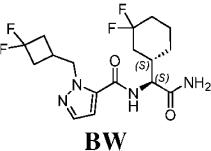
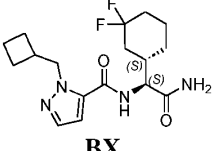
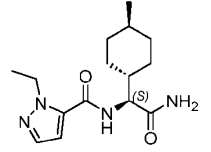
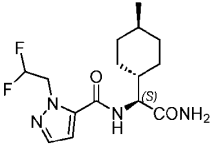
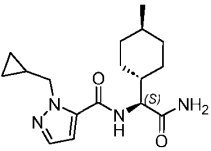
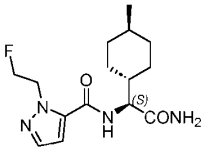
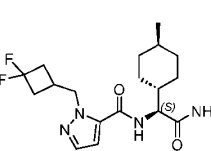
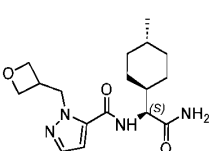
[0283] Intermediate **BK-1** was separated by prep-Achiral-SFC with the following conditions (Column: GreenSep Basic 3 *15 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MeOH (1%-2M-NH₃-MeOH); Flow rate: 65 mL/min; Gradient: isocratic 18% B; Column

Temperature (°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford the major peak as a mixture of **BK-2** and **BL-2**. The mixture was separated by SFC with the following conditions (Column: (S, S)-WHELK-O1 3 * 25 cm, 5 µm; Mobile Phase A: CO₂, Mobile Phase B: ACN: MeOH = 1: 1 (1% 2M NH₃-MEOH); Flow rate: 90 mL/min; Gradient: isocratic 14% B; Column Temperature(°C): 35; Back Pressure (bar): 100; Wave Length: 220 nm) to afford the first peak as (S)-N-((S)-cyano((S)-7-fluorochroman-4-yl)methyl)-2-methylpropane-2-sulfinamide (**BK-2**) and the second peak as (S)-N-((S)-cyano((R)-7-fluorochroman-4-yl)methyl)-2-methylpropane-2-sulfinamide (**BL-2**). LCMS (ESI, m/z): [M+H]⁺ 311.1.

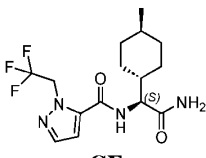
[0284] Following conditions analogous to synthesis of **BI**, Intermediate **BK** was synthesized from **BK-2** and Intermediate **BL** was synthesized from **BL-2**. LCMS (ESI, m/z): [M+H]⁺ 207.3.

[0285] The intermediates in the table below were synthesized using conditions analogous to synthesis of Intermediates **F**.

Intermediates	Name LCMS (ESI, m/z)	Intermediates	Name LCMS (ESI, m/z)
	(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-(methyl-d ₃)-1H-pyrazole-5-carboxamide [M+H] ⁺ 304.1		(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1H-pyrazole-5-carboxamide [M+H] ⁺ 351.1
	(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-(2-fluoroethyl)-1H-pyrazole-5-carboxamide [M+H] ⁺ 333.2		(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-4-methyl-1,2,5-oxadiazole-3-carboxamide [M+H] ⁺ 303.1
	(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-(cyclopropylmethyl)-1H-pyrazole-5-carboxamide [M+H] ⁺ 341.2		(S)-N-(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-(cyclobutylmethyl)-1H-pyrazole-5-carboxamide [M+H] ⁺ 355.2

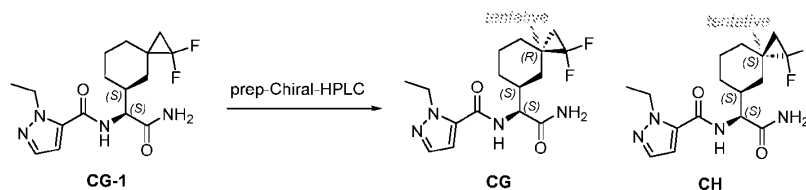
 BS	(<i>S</i>)- <i>N</i> -(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 391.3	 BT	<i>N</i> -((<i>S</i>)-2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-((<i>R</i> [*])-1-(3,3-difluorocyclobutyl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 405.3
 BU	(<i>S</i>)- <i>N</i> -(2-amino-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-5-cyano-1-methyl-1 <i>H</i> -pyrrole-2-carboxamide [<i>M</i> + <i>H</i>] ⁺ 325.0	 BV	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 357.1
 BW	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 391.3	 BX	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-(cyclobutylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 355.4
 BY	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 293.2	 BZ	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 329.2
 CA	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(cyclopropylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 319.2	 CB	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(2-fluoroethyl)-1 <i>H</i> -pyrazole-5-carboxamide [<i>M</i> + <i>H</i>] ⁺ 311.1
 CC	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide	 CD	<i>N</i> -((<i>S</i>)-2-amino-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide

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	[M+H] ⁺ 369.2		[M+H] ⁺ 335.2
 CF	<i>N</i>-((<i>S</i>)-2-amino-1-((1<i>R</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(2,2,2-trifluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide [M+H]⁺ 347.1		

Intermediates CG and CH

N-((*S*)-2-amino-1-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CG**) and *N*-((*S*)-2-amino-1-((3*S*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CH**)

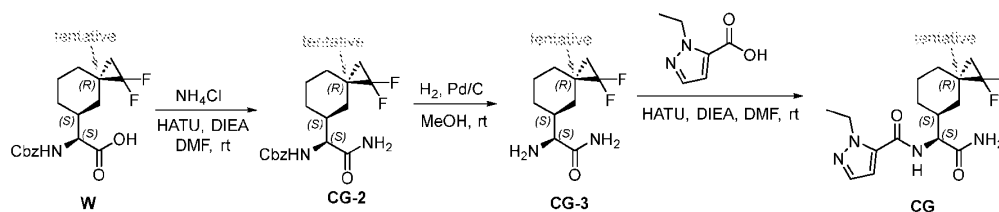


[0286] Following conditions analogous to synthesis of **F**, Intermediate **CG-1** was synthesized from **V**. Intermediate **CG-1** was separated by prep-Chiral-HPLC with the following conditions (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μ m; Mobile Phase A: Hex (0.5% 2 M NH₃-MeOH), Mobile Phase B: EtOH: DCM = 1: 1; Flow rate: 20 mL/min; Gradient (B%): isocratic 15; Wave Length: 254/220 nm) to afford Peak 1, which was tentatively assigned as *N*-((*S*)-2-amino-1-((3*S*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CH**), and peak 2, which was tentatively assigned as *N*-((*S*)-2-amino-1-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CG**). LCMS (ESI, *m/z*): [M+H]⁺ 341.1.

Intermediate CG (alternative synthesis)

N-((*S*)-2-amino-1-((3*R*,5*S*)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CG**)

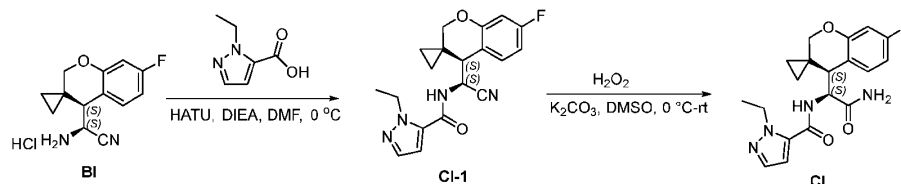
- 115 -



[0287] Following conditions analogous to synthesis of **F**, Intermediate **CG** was synthesized from Intermediate **W**, via amide coupling, Cbz deprotection and amide coupling. LCMS (ESI, m/z): $[M+H]^+$ 341.1.

Intermediate CI

N-((*S*)-2-amino-1-((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CI**)



Step 1: *N*-((*S*)-Cyano((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CI-1**)

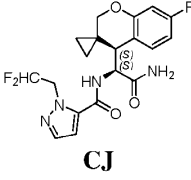
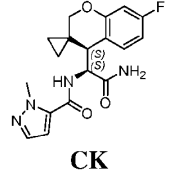
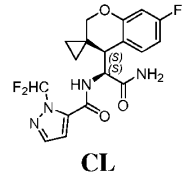
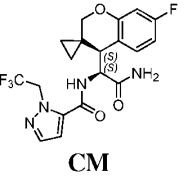
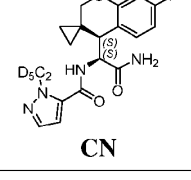
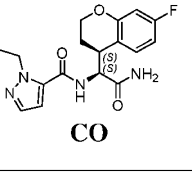
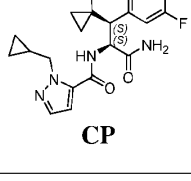
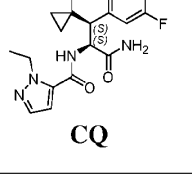
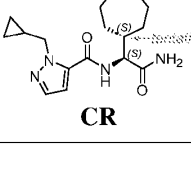
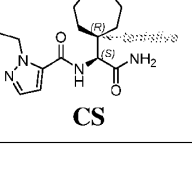
[0288] A mixture of (*S*)-2-amino-2-((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetonitrile hydrochloride (130 mg, 0.48 mmol), 1-ethyl-1*H*-pyrazole-5-carboxylic acid (78 mg, 0.56 mmol), DIEA (0.39 mL, 2.2 mmol) and HATU (319 mg, 0.84 mmol) in DMF (2 mL) was stirred for 2 hrs at 0 °C. The mixture was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel; mobile phase: ACN in Water (0.05% NH_4HCO_3), 10% to 50% gradient in 30 min) to afford *N*-((*S*)-cyano((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (150 mg). LCMS (ESI, m/z): $[M+H]^+$ 355.1.

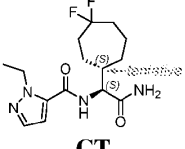
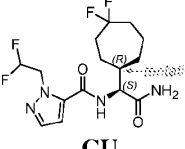
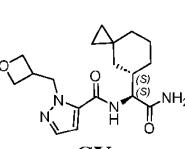
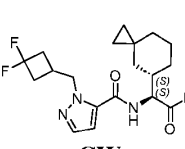
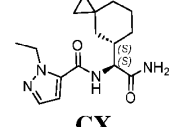
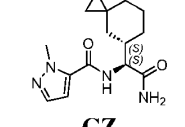
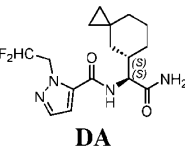
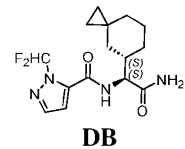
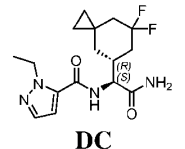
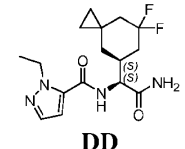
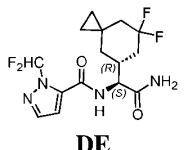
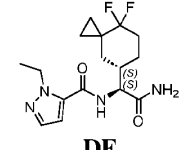
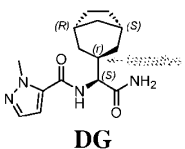
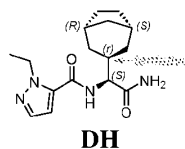
Step 2: *N*-((*S*)-2-Amino-1-((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**CI**)

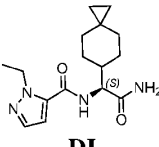
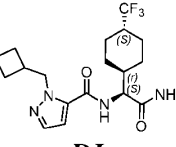
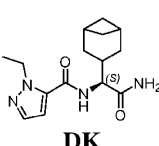
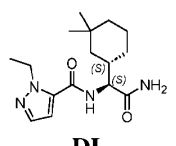
[0289] To a stirred mixture of *N*-((*S*)-cyano((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)methyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (150 mg, 0.42 mmol) and K_2CO_3 (175 mg, 1.3 mmol) in DMSO (1.5 mL) at 0 °C was added H_2O_2 (30% in H_2O , 0.5 g, 4.4 mmol) dropwise. After stirring for 2 hrs at rt, the mixture was treated with water and extracted with

EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/EtOAc (1:3), to afford Intermediate **CI** (150 mg). LCMS (ESI, m/z): $[\text{M}+\text{H}]^+$ 373.2.

[0290] Following conditions analogous to synthesis of **CI**, the intermediates in the table below were synthesized from the corresponding amino nitriles.

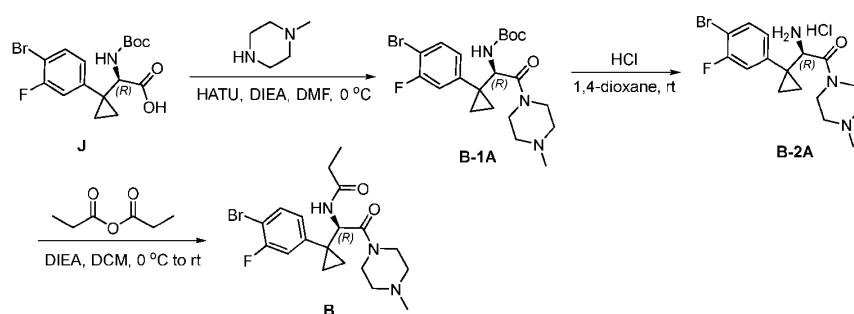
Int. #	Name LCMS (ESI, m/z)	Int. #	Name LCMS (ESI, m/z)
 CJ	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}-\text{H}]^-$ 407.2	 CK	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 359.1
 CL	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(difluoromethyl)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 395.2	 CM	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(2,2,2-trifluoroethyl)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}-\text{H}]^-$ 425.2
 CN	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(ethyl- d_5)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 378.2	 CO	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-7-fluorochroman-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 347.1
 CP	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-6,7-difluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(cyclopropylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 417.1	 CQ	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-6,7-difluorospiro-[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 391.1
 CR	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>S</i>)-4,4-difluorocyclo-heptyl)-2-oxoethyl)-1-(cyclopropylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 355.2	 CS	<i>N</i> -((<i>S</i>)-2-amino-1-((<i>R</i>)-4,4-difluorocyclo-heptyl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide $[\text{M}+\text{H}]^+$ 329.2

 CT	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>S</i>)-4,4-difluorocyclo-heptyl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamides [<i>M</i>+<i>H</i>]⁺ 329.1	 CU	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>R</i>)-4,4-difluorocyclo-heptyl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 365.1
 CV	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-(oxetan-3-ylmethyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 347.1	 CW	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-((3,3-difluorocyclobutyl)methyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 381.3
 CX	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 305.2	 CZ	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 291.2
 DA	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 341.1	 DB	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-(difluoromethyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 327.2
 DC	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>R</i>)-7,7-difluorospiro-[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 340.9	 DD	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>S</i>)-7,7-difluorospiro-[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 340.9
 DE	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>R</i>)-7,7-difluorospiro-[2.5]octan-5-yl)-2-oxoethyl)-1-(difluoromethyl)-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 363.2	 DF	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>S</i>)-8,8-difluorospiro-[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 341.2
 DG	<i>N</i>-((<i>S</i>)-2-amino-1-((1<i>R</i>,3<i>r</i>,5<i>S</i>)-bicyclo[3.2.1]octan-3-yl)-2-oxoethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 291.2	 DH	<i>N</i>-((<i>S</i>)-2-amino-1-((1<i>R</i>,3<i>r</i>,5<i>S</i>)-bicyclo[3.2.1]octan-3-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [<i>M</i>+<i>H</i>]⁺ 305.2

 DI	(<i>S</i>)-<i>N</i>-(2-amino-2-oxo-1-(spiro[2.5]octan-6-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [M+H]⁺ 305.1	 DJ	<i>N</i>-((<i>S</i>)-2-amino-2-oxo-1-((1<i>r</i>,4<i>S</i>)-4-(trifluoromethyl)cyclohexyl)ethyl)-1-(cyclobutylmethyl)-1<i>H</i>-pyrazole-5-carboxamide [M+H]⁺ 387.1
 DK	(<i>S</i>)-<i>N</i>-(2-amino-1-(bicyclo[3.1.1]heptan-3-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [M+H]⁺ 291.1	 DL	<i>N</i>-((<i>S</i>)-2-amino-1-((<i>S</i>)-3,3-dimethylcyclohexyl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide [M+H]⁺ 307.2

Intermediate **B** (alternative synthesis)

(*R*)-*N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**B**)



Step 1: *tert*-Butyl (*R*)-2-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)carbamate (**B-1A**)

[0291] A solution of (*R*)-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((*tert*-butoxycarbonyl)amino)acetic acid (5.0 g, 13 mmol), 1-methylpiperazine (1.4 g, 14 mmol), DIEA (9.0 mL, 52 mmol) and HATU (7.4 g, 19 mmol) in DMF (50 mL) was stirred for 1 hr at 0 °C under N₂. The mixture was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel; mobile phase: ACN in Water (10 mmol/L NH₄HCO₃), 20% to 60% gradient in 30 min) to afford *tert*-butyl (*R*)-2-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)carbamate (5.0 g). LCMS (ESI, *m/z*): [M+H]⁺ 470.1.

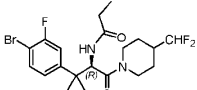
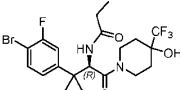
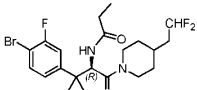
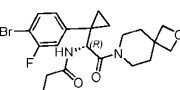
Step 2: (*R*)-2-Amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-1-(4-methylpiperazin-1-yl)ethan-1-one hydrochloride (**B-2A**)

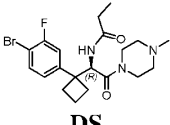
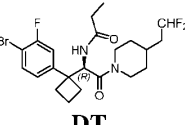
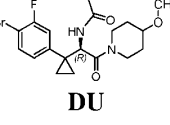
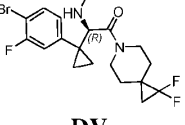
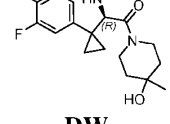
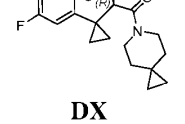
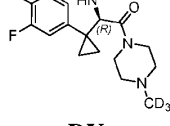
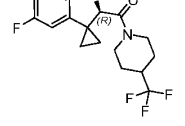
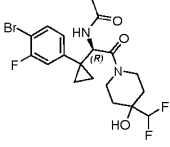
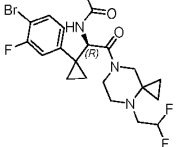
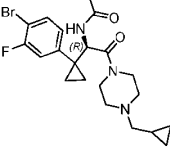
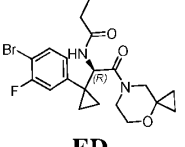
[0292] A mixture of *tert*-butyl (*R*)-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)carbamate (5 g, 11 mmol) and HCl solution (4.0 M in 1,4-dioxane, 50 mL) in 1,4-dioxane (50 mL) was stirred at rt for 1 hr. The mixture was concentrated under reduced pressure to afford (*R*)-2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-1-(4-methylpiperazin-1-yl)ethan-1-one as HCl salt. LCMS (ESI, *m/z*): [M+H]⁺ 370.1.

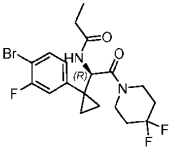
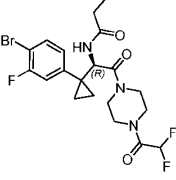
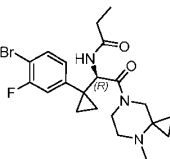
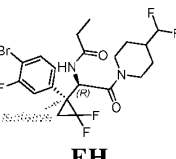
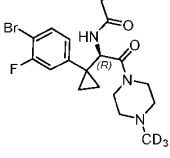
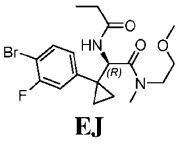
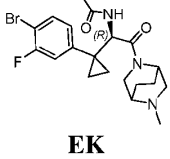
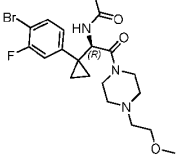
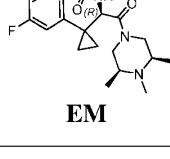
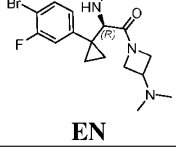
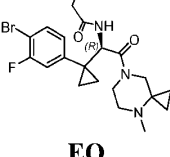
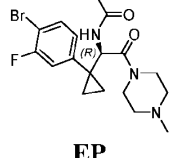
Step 3: (*R*)-*N*-(1-(1-(4-Bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**B**)

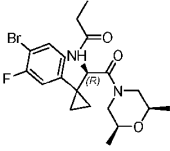
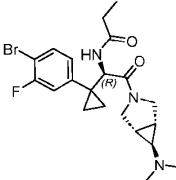
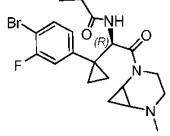
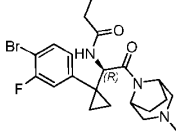
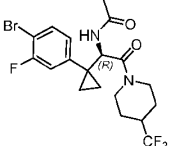
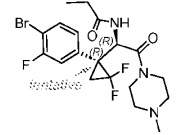
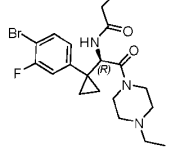
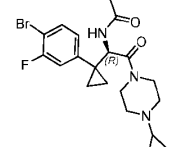
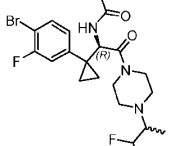
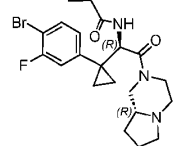
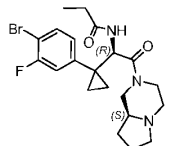
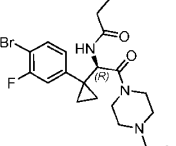
[0293] To solution of (*R*)-2-amino-2-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-1-(4-methylpiperazin-1-yl)ethan-1-one hydrochloride (5.0 g, 12 mmol) and DIEA (11.8 mL, 66 mmol) in DCM (50 mL) at 0 °C under N₂ was added propionic anhydride (3.5 g, 27 mmol). After stirring for 1 hr at rt, the mixture was treated with water and extracted with DCM. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (10:1), to afford Intermediate **B** (4 g). LCMS (ESI, *m/z*): [M+H]⁺ 426.1.

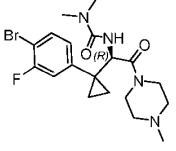
[0294] Following conditions analogous to synthesis of **B**, Intermediates **DN-FB** were synthesized from the corresponding amino acids. For Intermediate **FC**, acyl chloride was used instead of acid anhydride for the last step.

Int. #	Name LCMS (ESI, <i>m/z</i>)	Int. #	Name LCMS (ESI, <i>m/z</i>)
 DO	(<i>R</i>)- <i>N</i> -(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxoethyl)propionamide [M-H] ⁻ 459.2	 DP	(<i>R</i>)- <i>N</i> -(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)-2-oxoethyl)propionamide [M+H] ⁺ 495.2
 DQ	(<i>R</i>)- <i>N</i> -(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H] ⁺ 476.1	 DR	(<i>R</i>)- <i>N</i> -(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)ethyl)propionamide [M+H] ⁺ 453.1

 DS	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclobutyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 440.1	 DT	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclobutyl)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 490.2
 DU	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(difluoromethoxy)piperidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 477.2	 DV	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)propionamide [M+H]⁺ 472.9
 DW	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 441.1	 DX	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(6-azaspiro[2.5]octan-6-yl)ethyl)propionamide [M+H]⁺ 437.1
 DY	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(methyl-<i>d</i>₃)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 429.3	 DZ	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)propionamide [M+H]⁺ 479.1
 EA	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(difluoromethyl)-4-hydroxypiperidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 477.2	 EB	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(2,2-difluoroethyl)-4,7-diazaspiro[2.5]octan-7-yl)-2-oxoethyl)propionamide [M+H]⁺ 502.2
 EC	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(cyclopropylmethyl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 466.1	 ED	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)ethyl)propionamide [M+H]⁺ 439.0

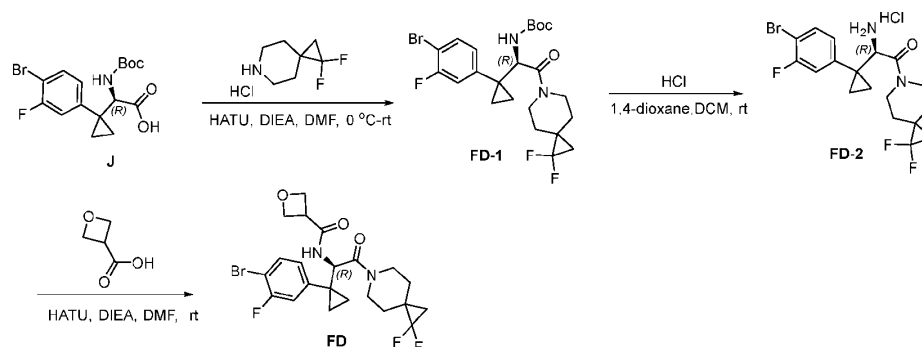
 EE	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4,4-difluoropiperidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 447.1	 EF	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(2,2-difluoroacetyl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 490.1
 EG	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.2	 EH	<i>N</i>-((<i>R</i>)-1-((<i>R</i>*)-1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 497.2
 EI	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(methyl-<i>d</i>₃)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 429.1	 EJ	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((2-methoxyethyl)(methyl)amino)-2-oxoethyl)propionamide [M+H]⁺ 415.1
 EK	<i>N</i>-((1<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.3	 EL	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(2-methoxyethyl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 470.1
 EM	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-((3<i>S</i>,5<i>R</i>)-3,4,5-trimethylpiperazin-1-yl)ethyl)propionamide [M+H]⁺ 454.2	 EN	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(3-(dimethylamino)azetidin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 426.1
 EO	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxoethyl)-2-methoxyacetamide [M+H]⁺ 468.2	 EP	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-2,2,2-trifluoroacetamide 466.1

 EQ	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((2<i>S</i>,6<i>R</i>)-2,6-dimethylmorpholino)-2-oxoethyl)propionamide [M-H]⁻ 439.1	 ER	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((1<i>R</i>,5<i>S</i>,6<i>S</i>)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.2
 ES	<i>N</i>-((1<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(5-methyl-2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-oxoethyl)propionamide [M+H]⁺ 438.1	 ET	<i>N</i>-((1<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.1
 EU	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)propionamide [M+H]⁺ 479.1	 EV	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)-2,2-difluorocyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 462.0
 EW	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-ethylpiperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 440.1	 EX	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-cyclopropylpiperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.1
 EY	<i>N</i>-((1<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-(1,1-difluoropropan-2-yl)piperazin-1-yl)-2-oxoethyl)propionamide [M+H]⁺ 490.2	 EZ	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((<i>R</i>)-hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1<i>H</i>)-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.1
 FA	<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-((<i>S</i>)-hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1<i>H</i>)-yl)-2-oxoethyl)propionamide [M+H]⁺ 452.1	 FB	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-oxo-2-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)ethyl)propionamide [M+H]⁺ 494.2

 FC	(<i>R</i>)-3-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1,1-dimethylurea [M+H]⁺ 441.0		
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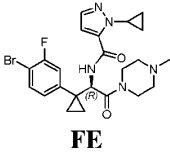
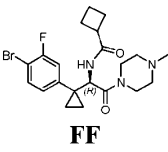
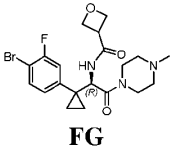
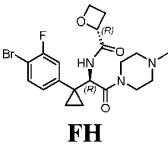
Intermediate FD

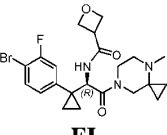
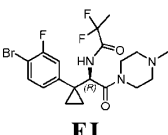
(*R*)-*N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)oxetane-3-carboxamide (FD)



[0295] Following conditions analogous to synthesis of **B-2A**, Intermediates **FD** was synthesized from **J**, via HATU-mediated amide coupling, Boc deprotection and HATU-mediated amide coupling. LCMS (ESI, *m/z*): [M+H]⁺ 501.1.

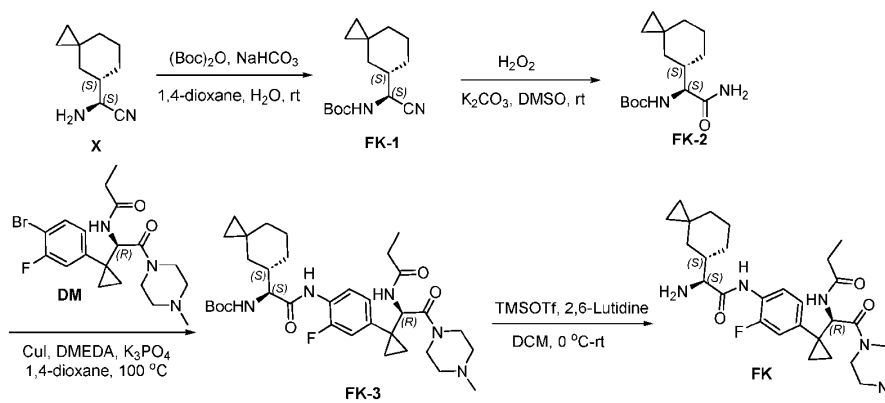
[0296] The intermediates in the table below were synthesized using conditions analogous to the synthesis of Intermediate **FD**.

Int. #	Name LCMS (ESI, <i>m/z</i>)	Int. #	Name LCMS (ESI, <i>m/z</i>)
 FE	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1H-pyrazole-5-carboxamide [M+H]⁺ 504.2	 FF	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclobutanecarboxamide [M+H]⁺ 452.3
 FG	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)oxetane-3-carboxamide [M+H]⁺ 454.1	 FH	(<i>R</i>)-<i>N</i>-((<i>R</i>)-1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)oxetane-2-carboxamide [M+H]⁺ 454.2

 FI	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxoethyl)oxetane-3-carboxamide [M+H]⁺ 480.0	 FJ	(<i>R</i>)-<i>N</i>-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-2,2-difluoropropanamide [M+H]⁺ 462.1
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Intermediate FK

N-((*R*)-1-(1-(4-((*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**FK**)



Step 1: *tert*-Butyl ((*S*)-cyano((*S*)-spiro[2.5]octan-5-yl)methyl)carbamate (**FK-1**)

[0297] A solution of (*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetonitrile (4.0 g, 24 mmol), (Boc)₂O (10.6 g, 49 mmol) and NaHCO₃ (6.1 g, 73 mmol) in 1,4-dioxane (40 mL) and H₂O (5 mL) was stirred at rt for 1 hr. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (5:1), to afford *tert*-butyl ((*S*)-cyano((*S*)-spiro[2.5]octan-5-yl)methyl)carbamate (4.0 g). LCMS (ESI, *m/z*): [M+H]⁺ 209.

Step 2: *tert*-Butyl ((*S*)-2-amino-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (**FK-2**)

[0298] To a mixture of *tert*-butyl ((*S*)-cyano((*S*)-spiro[2.5]octan-5-yl)methyl)carbamate (3.0 g, 11 mmol) and K₂CO₃ (1.6 g, 11 mmol) in DMSO (30 mL) at rt was added H₂O₂ (30% in H₂O, 2.6 g, 23 mmol) dropwise. After stirring for 4 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford *tert*-

butyl ((*S*)-2-amino-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (3.0 g). LCMS (ESI, *m/z*): [M+H]⁺ 283.1.

Step 3: *tert*-Butyl ((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (**FK-3**)

[0299] A mixture of *tert*-butyl ((*S*)-2-amino-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (1.6 g, 5.7 mmol), (*R*)-*N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (2.4 g, 5.6 mmol), K₃PO₄ (2.4 g, 11 mmol), DMEDA (500 mg, 5.7 mmol) and CuI (1.1 g, 5.8 mmol) in 1,4-dioxane (40 mL) was degassed and backfilled with N₂. After stirring at 100 °C for 6 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel, 90 g; mobile phase, MeCN in water (0.05% NH₄HCO₃), 40% to 60% gradient in 30 min) to afford *tert*-butyl ((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (2.0 g). LCMS (ESI, *m/z*): [M+H]⁺ 628.5.

Step 4: *N*-(1-((*R*)-1-(1-(4-((*S*)-2-Amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**FK**)

[0300] To a stirred solution of *tert*-butyl ((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (2.0 g, 3.2 mmol) and 2,6-dimethylpyridine (4.1 g, 38 mmol) in DCM (20 mL) at 0 °C under N₂ was added TMSOTf (7.1 g, 32 mmol) dropwise. After stirring at rt for 1 hr, the mixture was treated with water and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions (column: C18 silica gel; mobile phase: MeCN in water (0.05% NH₄HCO₃), 30% to 60% gradient in 30 min) to afford Intermediate **FK** (1.6 g). LCMS (ESI, *m/z*): [M+H]⁺ 528.4.

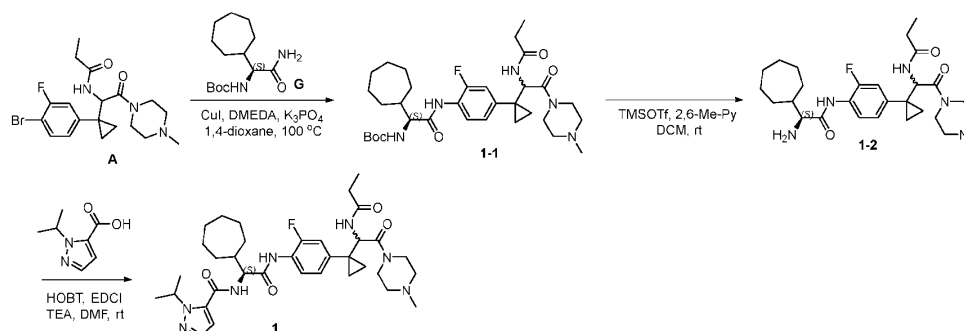
[0301] Following conditions analogous to synthesis of **FK**, Intermediate **FL** was synthesized from **X** and Intermediate **FM** from **BI**. Intermediate **FN** was synthesized following the last two steps, reacting **F-1** with **B**, followed by Boc deprotection. Intermediates **FO-FQ** were synthesized following the last two steps, reacting the precursor of **BV** with the corresponding bromide, followed by Boc deprotection.

Int. #	Structure	Name	LCMS (ESI, m/z)
FL		N-((R)-1-(1-(4-((S)-2-amino-2-((S)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide	[M+H] ⁺ 528.4
FM		N-((R)-1-(1-(4-((S)-2-amino-2-((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide	[M+H] ⁺ 596.4
FN		N-((R)-1-(1-(4-((S)-2-amino-2-(4,4-difluorocyclohexyl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide	[M+H] ⁺ 538.4
FO		N-((R)-1-(1-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxoethyl)propionamide	[M+H] ⁺ 573.2
FP		N-((R)-1-(1-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)-3-fluorophenyl)cyclopropyl)-2-oxo-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)propionamide	[M+H] ⁺ 591.4
FQ		N-((R)-1-(1-(4-((S)-2-amino-2-((S)-3,3-difluorocyclohexyl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)propionamide	[M+H] ⁺ 585.5

Example 1

N-((1S)-1-cycloheptyl-2-((2-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1H-pyrazole-5-carboxamide (1)

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Step 1: *tert*-Butyl ((1*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)carbamate (**1-1**)

[0302] To a stirred mixture of *N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (200 mg, 0.47 mmol), *tert*-butyl (*S*)-(2-amino-1-cycloheptyl-2-oxoethyl)carbamate (152 mg, 0.56 mmol) and *N*¹,*N*²-dimethylethane-1,2-diamine (41 mg, 0.47 mmol) in 1,4-dioxane (4 mL) was added CuI (89 mg, 0.47 mmol) and K₃PO₄ (209 mg, 0.99 mmol) at rt under N₂. The mixture was degassed, then stirred for 2 hrs at 100 °C under N₂. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (10:1), to afford *tert*-butyl ((1*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)carbamate (200 mg). LCMS (ESI, *m/z*): [M+H]⁺ 616.5.

Step 2: *N*-(1-(1-(4-((*S*)-2-amino-2-cycloheptylacetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**1-2**)

[0303] To a stirred solution of *tert*-butyl ((1*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)carbamate (100 mg, 0.16 mmol) in DCM (2 mL) at 0 °C under N₂ was added TMSOTf (360 mg, 1.62 mmol) and 2,6-dimethylpyridine (208 mg, 1.94 mmol) dropwise. After stirring for 20 min, the mixture was concentrated under reduced pressure to afford the crude product which was used in the next step directly. LCMS (ESI, *m/z*): [M+H]⁺ 516.4.

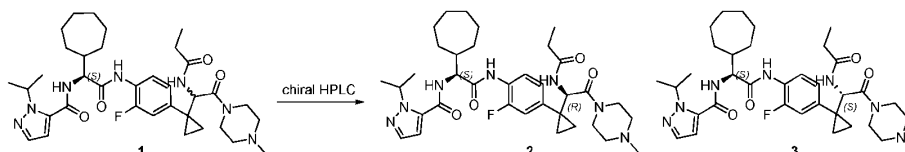
Step 3: *N*-((1*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1*H*-pyrazole-5-carboxamide (**1**)

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[0304] To a stirred mixture of *N*-(1-(1-(4-((*S*)-2-amino-2-cycloheptylacetyl)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (90 mg, 0.17 mmol) and 1-isopropyl-1*H*-pyrazole-5-carboxylic acid (40 mg, 0.26 mmol) in DMF (1 mL) at rt under N₂ were added HOBt (35 mg, 0.26 mmol), EDCI (50 mg, 0.26 mmol) and TEA (70 mg, 0.70 mmol). After stirring for 1 hr, the mixture was purified directly by prep-HPLC (0.05% NH₄HCO₃) to afford Example 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.71 (t, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.20-7.11 (m, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 5.38 (m, 1H), 5.19 (d, *J* = 8.8 Hz, 1H), 4.61 (t, *J* = 8.4 Hz, 1H), 3.45-3.27 (m, 4H), 2.29-2.07 (m, 9H), 1.98 (m, 1H), 1.79-1.34 (m, 18H), 1.03-0.94 (m, 4H), 0.89-0.72 (m, 2H), 0.61 (m, 1H); LCMS (ESI, *m/z*): [M+H]⁺ 652.6.

Examples 2 and 3

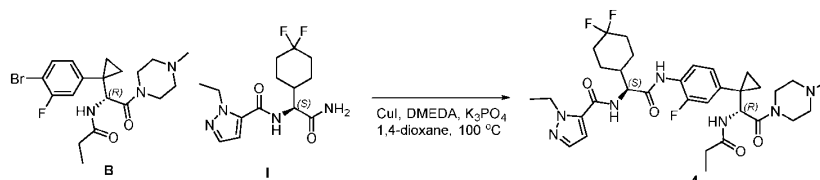
N-((*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1*H*-pyrazole-5-carboxamide (**2**) and *N*-((*S*)-1-cycloheptyl-2-((2-fluoro-4-(1-((*S*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1*H*-pyrazole-5-carboxamide (**3**)



[0305] Example 1 was further separated by chiral-HPLC with the following conditions (CHIRALPAK IG column, NH₄OH) to afford Examples 2 and 3. Example 2 (peak 2): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.71 (t, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.19-7.12 (m, 2H), 6.91 (d, *J* = 1.6 Hz, 1H), 5.38 (m, 1H), 5.19 (d, *J* = 8.8 Hz, 1H), 4.61 (t, *J* = 8.4 Hz, 1H), 3.48-3.28 (m, 4H), 2.25-2.05 (m, 9H), 1.95 (m, 1H), 1.77-1.32 (m, 18H), 1.01-0.93 (m, 4H), 0.90-0.70 (m, 2H), 0.61 (m, 1H); LCMS (ESI, *m/z*): [M+H]⁺ 652.6. Example 3 (peak 1): ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.71 (t, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 7.19-7.12 (m, 2H), 6.91 (d, *J* = 2 Hz, 1H), 5.42 - 5.35 (m, 1H), 5.19 (d, *J* = 8.8 Hz, 1H), 4.61 (t, *J* = 8.4 Hz, 1H), 3.48-3.28 (m, 4H), 2.25-2.05 (m, 9H), 1.95 (m, 1H), 1.77-1.32 (m, 18H), 1.01-0.93 (m, 4H), 0.90-0.70 (m, 2H), 0.61 (m, 1H); LCMS (ESI, *m/z*): [M+H]⁺ 652.6.

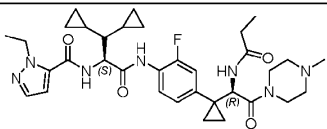
Example 4

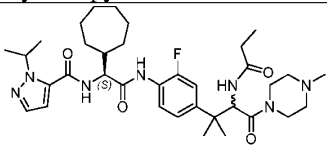
N-((*S*)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide

(4)

[0306] To a mixture of (*R*)-*N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (20.0 mg, 0.047 mmol), (*S*)-2-(4,4-difluorocyclohexyl)-2-[(2-ethylpyrazol-3-yl)formamido]acetamide (18.0 mg, 0.056 mmol), CuI (9 mg, 0.05 mmol) and K₃PO₄ (21.0 mg, 0.099 mmol) in 1,4-dioxane (0.5 mL) under N₂ was added DMEDA (4 mg, 0.05 mmol). The mixture was degassed, then stirred for 16 h at 100 °C under N₂. After completion, the reaction mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM/MeOH = 7:1) to afford impure product. The material was further purified by prep-HPLC (0.055% NH₄HCO₃) to afford Example 4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 8.59 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.73 (m, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.25-7.08 (m, 2H), 7.00 (d, *J* = 2.0 Hz, 1H), 5.17 (d, *J* = 8.8 Hz, 1H), 4.65 (t, *J* = 8.4 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 3.46-3.29 (m, 4H), 2.26-1.66 (m, 16H), 1.55-1.32 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.03-0.91 (m, 4H), 0.88-0.72 (m, 2H), 0.60 (m, 1H); LCMS (ESI, *m/z*): [M+H]⁺ 660.3.

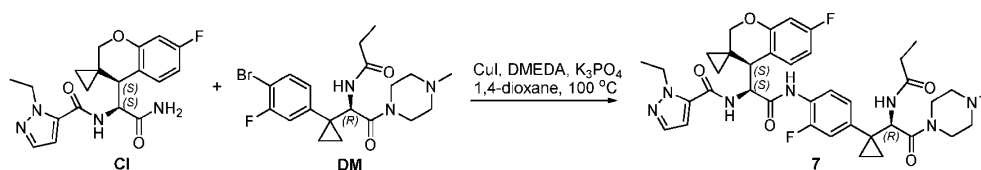
[0307] Examples 5 and 6 were synthesized using conditions analogous to synthesis of Example 4, from Intermediate B or E.

Ex. #	Structure Name	Spectral data
5	 <i>N</i> -((<i>S</i>)-1,1-dicyclopropyl-3-((2-fluoro-4-(1-((<i>R</i>)-2-(4-	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.41 (d, <i>J</i> = 9.2 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.78 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.11 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.96 (t, <i>J</i> = 8.0 Hz, 1H), 4.52-4.42 (m,

	methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-3-oxopropan-2-yl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	2H), 3.45-3.25 (m, 4H), 2.28-2.07 (m, 8H), 1.98 (m, 1H), 1.32-1.21 (m, 4H), 1.05-0.71 (m, 9H), 0.62 (m, 1H), 0.49-0.10 (m, 7H); LCMS (ESI, m/z): [M+H] ⁺ 636.7.
6	 <i>N</i> -((1 <i>S</i>)-1-cycloheptyl-2-((2-fluoro-4-(2-methyl-4-(4-methylpiperazin-1-yl)-4-oxo-3-propionamidobutan-2-yl)phenyl)amino)-2-oxoethyl)-1-isopropyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 7.97 (d, <i>J</i> = 9.2 Hz, 1H), 7.75 (m, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.25-7.16 (m, 2H), 6.92 (d, <i>J</i> = 2.0 Hz, 1H), 5.39 (m, 1H), 5.08 (d, <i>J</i> = 9.2 Hz, 1H), 4.62 (t, <i>J</i> = 8.4 Hz, 1H), 3.43-3.12 (m, 4H), 2.22-2.02 (m, 9H), 1.88 (m, 1H), 1.78-1.26 (m, 24H), 0.93 (t, <i>J</i> = 7.6 Hz, 3H); LCMS (ESI, m/z): [M+H] ⁺ 654.7.

Example 7

1-ethyl-*N*-((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-1-((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1*H*-pyrazole-5-carboxamide (7)

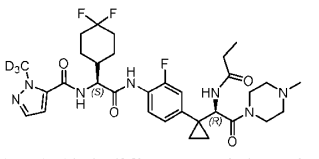
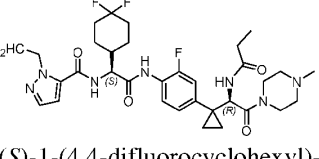
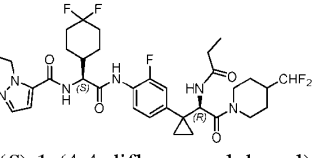


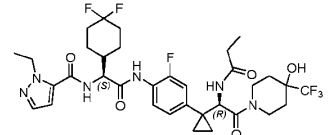
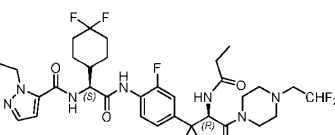
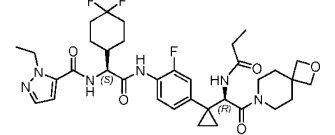
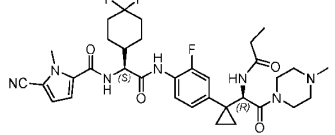
[0308] A mixture of *N*-((*S*)-2-amino-1-((*S*)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (61 mg, 0.16 mmol), (*R*)-*N*-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (70 mg, 0.16 mmol), CuI (31 mg, 0.16 mmol), DMEDA (14 mg, 0.16 mmol) and K₃PO₄ (73 mg, 0.34 mmol) in 1,4-dioxane (0.8 mL) was degassed and backfilled with N₂. After stirring at 100 °C for 6 hrs, the mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM/MeOH = 10:1) to afford impure product. The material was further purified by prep-HPLC (0.05% NH₄HCO₃) to afford Example 7. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 8.91 (d, *J* = 9.2 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.30-7.16 (m, 3H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.63-6.59 (m, 1H), 6.52-6.48 (m, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 5.13-5.05 (m, 2H), 4.32 (m, 2H), 3.50-3.31 (m, 5H), 2.57-2.53 (m, 1H), 2.25-

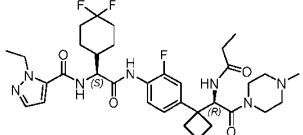
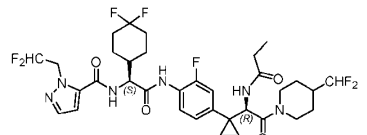
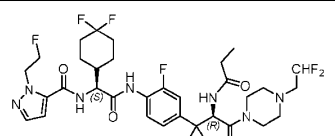
- 131 -

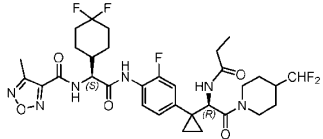
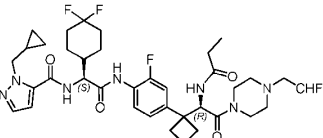
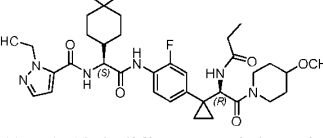
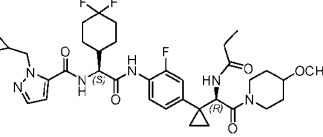
1.95 (m, 9H), 1.15 (t, $J = 7.2$ Hz, 3H), 1.05-0.92 (m, 4H), 0.90-0.75 (m, 3H), 0.68-0.48 (m, 3H), 0.32-0.25 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 718.3.

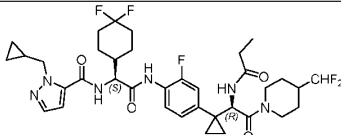
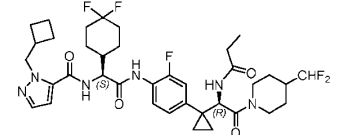
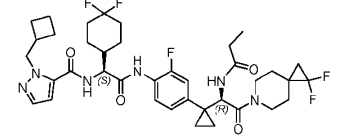
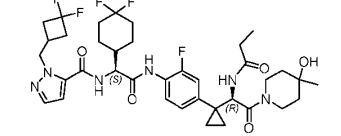
[0309] Examples in the table below were synthesized using conditions analogous to synthesis of Example 7.

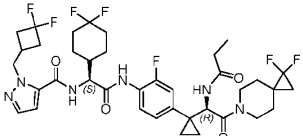
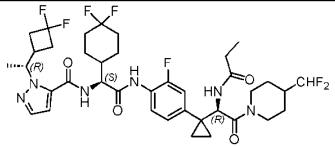
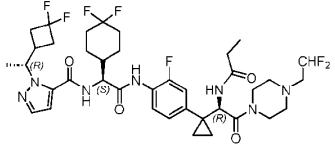
Ex. #	Structure Name	Spectral data
8	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(methyl-d_3)-1<i>H</i>-pyrazole-5-carboxamide	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.97 (s, 1H), 8.55 (d, $J = 8.4$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.71 (dd, $J = 8.4$ Hz, 8.4 Hz, 1H), 7.44 (d, $J = 2.0$ Hz, 1H), 7.20-7.09 (m, 2H), 7.02 (d, $J = 2.0$ Hz, 1H), 5.17 (d, $J = 8.4$ Hz, 1H), 4.64-4.62 (dd, $J = 8.4$ Hz, 8.4 Hz, 1H), 3.30-3.38 (m, 4H), 2.25-1.92 (m, 12H), 1.90-1.62 (m, 4H), 1.50-1.27 (m, 2H), 0.98-0.91 (m, 4H), 0.85-0.81 (m, 1H), 0.77-0.73 (m, 1H), 0.60-0.58 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 649.6.
9	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.99 (s, 1H), 8.75 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 8.8$ Hz, 1H), 7.72 (dd, $J = 8.4$ Hz, 8.4 Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.19-7.11 (m, 3H), 6.45-6.17 (m, 1H), 5.17 (d, $J = 8.8$ Hz, 1H), 4.99-4.91 (m, 2H), 4.68 (dd, $J = 8.4$ Hz, 8.4 Hz, 1H), 3.45-3.32 (m, 4H), 2.23-1.91 (m, 12H), 1.89-1.67 (m, 4H), 1.52-1.28 (m, 2H), 1.00-0.93 (m, 4H), 0.88-0.80 (m, 1H), 0.78-0.72 (m, 1H), 0.62-0.55 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 696.6.
10	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.97 (d, $J = 9.2$ Hz, 1H), 8.58 (d, $J = 8.0$ Hz, 1H), 8.08-7.96 (m, 1H), 7.79-7.67 (m, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.22-7.13 (m, 2H), 7.01-6.99 (m, 1H), 6.87 (m, 1H), 5.22-5.15 (m, 1H), 4.77-4.62 (m, 1H), 4.53-4.41 (m, 2H), 4.39-4.31 (m, 1H), 3.95-3.82 (m, 1H), 3.04-2.88 (m, 1H), 2.58-2.56 (m, 1H), 2.22-1.96 (m, 6H), 1.95-1.57 (m, 6H), 1.55-1.25 (m, 5H), 1.24-1.03 (m, 2H), 0.96 (t, $J = 7.6$ Hz, 3H), 0.90-0.86 (m, 1H), 0.85-0.69 (m, 2H), 0.66-0.58 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 695.7.

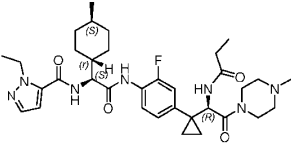
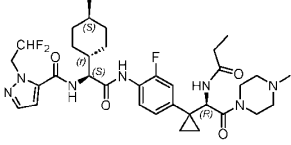
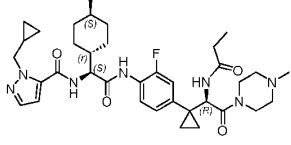
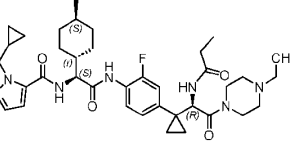
11	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-hydroxy-4-(trifluoromethyl)-piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96-9.93 (m, 1H), 8.60-8.56 (m, 1H), 8.12-7.97 (m, 1H), 7.88-7.65 (m, 1H), 7.48 (d, <i>J</i> = 1.6 Hz, 1H), 7.24-7.14 (m, 2H), 6.99 (m, 1H), 6.09-6.03 (m, 1H), 5.27-5.12 (m, 1H), 4.68-4.65 (m, 1H), 4.49-4.44 (m, 2H), 4.30-4.27 (m, 1H), 3.81-3.75 (m, 1H), 3.19-3.13 (m, 1H), 2.80-2.65 (m, 1H), 2.20-1.92 (m, 5H), 1.89-1.34 (m, 9H), 1.30-1.24 (m, 4H), 0.96 (q, <i>J</i> = 10.4 Hz, 3H), 0.88-0.86 (m, 1H), 0.82-0.70 (m, 2H), 0.69-0.53 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 729.6.
12	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.59 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.73-7.69 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.13 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 6.24-5.96 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.67-4.63 (m, 1H), 4.49-4.44 (m, 2H), 3.46-3.34 (m, 4H), 2.73-2.65 (m, 2H), 2.46-2.41 (m, 2H), 2.21-2.11 (m, 3H), 2.10-1.95 (m, 3H), 1.91-1.71 (m, 4H), 1.52-1.34 (m, 2H), 1.30-1.25 (m, 4H), 1.06-0.92 (m, 4H), 0.87-0.83 (m, 1H), 0.79-0.74 (m, 1H), 0.66-0.59 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 710.3.
13	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.59 (d, <i>J</i> = 8.0 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (dd, <i>J</i> = 8.4 Hz, 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.66-4.62 (m, 1H), 4.49-4.44 (m, 2H), 4.27-4.23 (m, 4H), 3.32-3.25 (m, 4H), 2.18-2.02 (m, 5H), 1.99-1.87 (m, 2H), 1.85-1.59 (m, 5H), 1.57-1.30 (m, 3H), 1.28-1.24 (t, <i>J</i> = 7.2 Hz, 3H), 0.99-0.91 (m, 4H), 0.86-0.83 (m, 1H), 0.77-0.73 (m, 1H), 0.63-0.59 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 687.3.
14	 5-cyano-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 8.57 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (dd, <i>J</i> = 8.4 Hz, <i>J</i> = 8.4 Hz, 1H), 7.20-7.12 (m, 2H), 7.05 (d, <i>J</i> = 2.0 Hz, 1H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.65 (dd, <i>J</i> = 8.4 Hz, <i>J</i> = 8.4 Hz, 1H), 3.94 (s, 3H), 3.45-3.32 (m, 4H), 2.25-

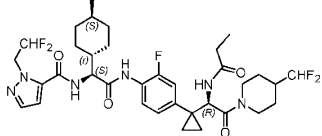
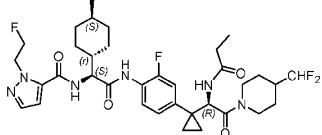
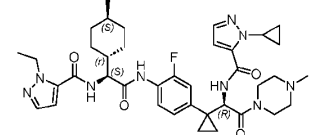
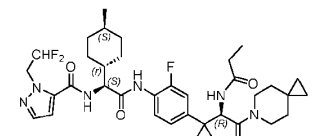
	oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-methyl-1 <i>H</i> -pyrrole-2-carboxamide	1.99 (m, 12H), 1.92-1.63 (m, 4H), 1.53-1.42 (m, 1H), 1.40-1.28 (m, 1H), 1.03-0.92 (m, 4H), 0.88-0.82 (m, 1H), 0.80-0.73 (m, 1H), 0.67-0.59 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 670.3.
15	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclobutyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.00 (s, 1H), 8.59 (d, <i>J</i> = 8.4 Hz, 1H), 8.36 (d, <i>J</i> = 9.2 Hz, 1H), 7.83 (dd, <i>J</i> = 8.4 Hz, 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.11-7.05 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 4.96 (d, <i>J</i> = 9.2 Hz, 1H), 4.68 (dd, <i>J</i> = 8.0 Hz, <i>J</i> = 8.0 Hz, 1H), 4.47 (q, <i>J</i> = 7.2 Hz, 2H), 3.42-3.39 (m, 1H), 3.12-3.00 (m, 3H), 2.88-2.85 (m, 1H), 2.34-2.14 (m, 5H), 2.10-1.99 (m, 5H), 1.97 (s, 3H), 1.90-1.63 (m, 7H), 1.52-1.48 (m, 1H), 1.40-1.30 (m, 2H), 1.28 (t, <i>J</i> = 7.2 Hz, 3H), 1.02 (t, <i>J</i> = 7.6 Hz, 3H); LCMS (ESI, m/z): [M+H] ⁺ 674.4.
16	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclo-propyl)-2-fluorophenyl)amino)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.00 (m, 1H), 8.76 (d, <i>J</i> = 8.4 Hz, 1H), 8.08-7.96 (m, 1H), 7.77-7.66 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.13 (m, 3H), 6.48-6.16 (m, 1H), 6.05-5.60 (m, 1H), 5.24-5.15 (m, 1H), 5.02-4.93 (m, 2H), 4.72-4.67 (m, 1H), 4.40-4.32 (m, 1H), 3.99-3.80 (m, 1H), 3.03-2.89 (m, 1H), 2.56-2.50 (m, 1H), 2.20-1.92 (m, 6H), 1.89-1.56 (m, 6H), 1.52-1.34 (m, 2H), 1.30-1.02 (m, 2H), 0.97-0.94 (t, <i>J</i> = 7.2 Hz, 3H), 0.88-0.55 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 731.3.
17	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclo-propyl)-2-fluorophenyl)amino)-2-oxoethyl)-1-(2-fluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.66 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.71 (t, <i>J</i> = 8.4 Hz, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 6.31-5.92 (m, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.88-4.71 (m, 3H), 4.69-4.63 (m, 2H), 3.48-3.35 (m, 4H), 2.69 (m, 2H), 2.49-2.28 (m, 3H), 2.23-1.98 (m, 6H), 1.92-1.69 (m, 4H), 1.54-1.29 (m, 2H), 1.02-0.97 (m, 4H), 0.88-0.82 (m, 1H), 0.79-0.72 (m, 1H), 0.63-0.59 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 728.6.

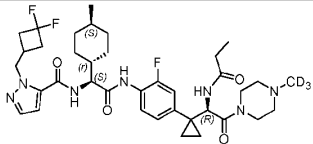
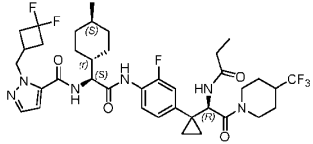
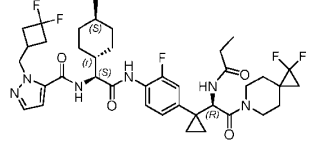
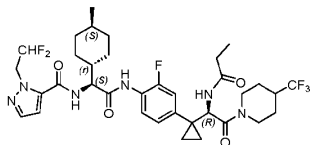
18	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-4-methyl-1,2,5-oxadiazole-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.05 (m, 1H), 9.21 (d, <i>J</i> = 8.0 Hz, 1H), 8.09-7.96 (m, 1H), 7.79-7.68 (m, 1H), 7.23-7.14 (m, 2H), 6.08-5.62 (m, 1H), 5.25-5.15 (m, 1H), 4.75-4.72 (m, 1H), 4.36-4.32 (m, 1H), 3.89-3.86 (m, 1H), 2.98-2.90 (m, 1H), 2.64-2.56 (m, 1H), 2.48 (s, 3H), 2.19-1.89 (m, 6H), 1.87-1.59 (m, 6H), 1.50-1.04 (m, 4H), 0.98-0.58 (m, 7H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 683.3.
19	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclobutyl)-2-fluorophenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.03 (s, 1H), 8.64 (d, <i>J</i> = 8.4 Hz, 1H), 8.37 (d, <i>J</i> = 9.2 Hz, 1H), 7.77 (t, <i>J</i> = 8.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.11-7.06 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 6.15-5.87 (m, 1H), 4.97 (d, <i>J</i> = 8.0 Hz, 1H), 4.66 (t, <i>J</i> = 8.4 Hz, 1H), 4.34 (d, <i>J</i> = 7.2 Hz, 2H), 3.45-3.42 (m, 1H), 3.08-3.04 (m, 3H), 2.90-2.83 (m, 1H), 2.59-2.53 (m, 2H), 2.42-2.38 (m, 1H), 2.34-2.16 (m, 5H), 2.11-1.88 (m, 6H), 1.82-1.48 (m, 7H), 1.40-1.30 (m, 1H), 1.22-1.15 (m, 1H), 1.02 (t, <i>J</i> = 7.6 Hz, 3H), 0.42-0.38 (m, 2H), 0.33-0.29 (m, 2H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 750.4.
20	 <i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethoxy)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1-(2,2-difluoroethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.80-8.72 (m, 1H), 8.09-8.01 (m, 1H), 7.76-7.63 (m, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.21 (d, <i>J</i> = 12.0 Hz, 1H), 7.15-7.13 (m, 2H), 6.72 (t, <i>J</i> = 76.4 Hz, 1H), 6.48-6.15 (m, 1H), 5.20-5.11 (m, 1H), 5.03-4.90 (m, 2H), 4.72-4.62 (m, 1H), 4.39-4.22 (m, 1H), 3.89-3.51 (m, 2H), 3.31-3.00 (m, 2H), 2.21-1.96 (m, 5H), 1.92-1.66 (m, 6H), 1.53-1.31 (m, 4H), 0.99-0.74 (m, 6H), 0.69-0.60 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 747.6.
21	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethoxy)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclobutyl)-2-fluorophenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.65-8.62 (m, 1H), 8.08-8.03 (m, 1H), 7.75-7.66 (m, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.21 (d, <i>J</i> = 12.0 Hz, 1H), 7.14 (d, <i>J</i> = 8.4 Hz, 1H), 6.95 (d, <i>J</i> = 2.0 Hz, 1H), 6.72 (t, <i>J</i> = 76.4 Hz, 1H), 5.16-5.14 (m, 1H), 4.68-4.62 (m, 1H), 4.36-4.28 (m, 3H), 3.80-3.52 (m, 2H), 3.28-3.02 (m, 2H), 2.23-1.96 (m, 5H),

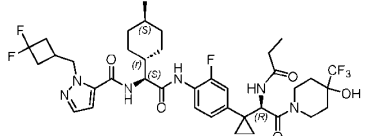
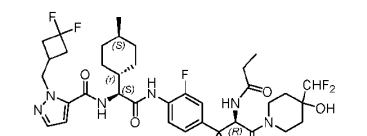
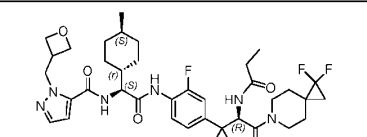
	2-oxo-1-(propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	1.92-1.75 (m, 6H), 1.52-1.32 (m, 4H), 1.24-1.18 (m, 1H), 0.98-0.93 (m, 4H), 0.89-0.74 (m, 2H), 0.66-0.59 (m, 1H), 0.42-0.38 (m, 2H), 0.33-0.29 (m, 2H); LCMS (ESI, m/z): [M+H] ⁺ 737.4.
22	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-(propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (m, 1H), 8.63 (d, <i>J</i> = 6.8 Hz, 1H), 8.08-7.96 (m, 1H), 7.78-7.66 (m, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.12 (m, 2H), 6.98 (m, 1H), 6.07-5.61 (m, 1H), 5.21-5.13 (m, 1H), 4.68-4.59 (m, 1H), 4.40-4.38 (m, 3H), 3.88 (m, 1H), 3.02-2.88 (m, 1H), 2.61-2.55 (m, 1H), 2.20-1.96 (m, 6H), 1.91-1.56 (m, 6H), 1.51-1.02 (m, 5H), 0.99-0.58 (m, 7H), 0.42-0.27 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 721.7.
23	 1-(cyclobutylmethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-(propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (m, <i>J</i> = 10.0 Hz, 1H), 8.63-8.60 (m, 1H), 8.08-7.96 (m, 1H), 7.76-7.66 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.25-7.09 (m, 2H), 6.97-6.95 (m, 1H), 6.09-5.60 (m, 1H), 5.19 (m, 1H), 4.70-4.61 (m, 1H), 4.57-4.51 (d, <i>J</i> = 10.8 Hz, 2H), 4.38-4.33 (m, 1H), 3.92-3.85 (m, 1H), 3.01-2.89 (m, 1H), 2.71-2.62 (m, 1H), 2.58-2.53 (m, 1H), 2.24-1.94 (m, 6H), 1.92-1.55 (m, 12H), 1.51-1.03 (m, 4H), 0.98-0.95 (t, <i>J</i> = 7.2 Hz, 3H), 0.91-0.59 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 735.4.
24	 1-(cyclobutylmethyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-(propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96 (s, 1H), 8.62 (d, <i>J</i> = 6.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.76-7.66 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.13 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.64 (m, 1H), 4.56-4.46 (m, 2H), 3.70-3.20 (m, 4H), 2.67 (m, 1H), 2.22-1.95 (m, 5H), 1.90-1.68 (m, 10H), 1.65-1.20 (m, 8H), 1.02-0.85 (m, 5H), 0.83-0.76 (m, 1H), 0.69-0.60 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 747.6.
25		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (m, 1H), 8.68 (d, <i>J</i> = 8.4 Hz, 1H), 8.03-7.94 (m, 1H), 7.80-7.67 (m, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.12 (m, 2H), 7.04-7.03 (m, 1H), 5.24-5.15 (m, 1H), 4.66-4.60 (m, 3H), 4.37-

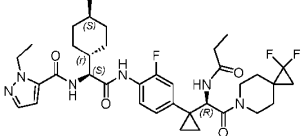
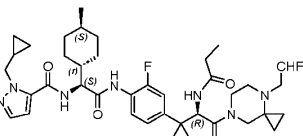
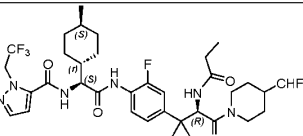
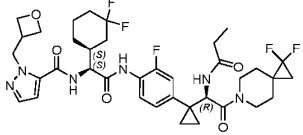
	1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	4.33 (d, <i>J</i> = 16.8 Hz, 1H), 3.96-3.87 (m, 1H), 3.54-3.43 (m, 1H), 3.27-3.20 (m, 1H), 2.97-2.91 (m, 1H), 2.62-2.52 (m, 3H), 2.48-2.38 (m, 2H), 2.21-1.96 (m, 5H), 1.89-1.70 (m, 4H), 1.52-1.22 (m, 5H), 1.15-1.03 (m, 3H), 1.00-0.72 (m, 7H), 0.65-0.55 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 751.6.
26	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-(4,4-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 8.70-8.65 (m, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.76-7.66 (m, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.14 (m, 2H), 7.04 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.70-4.58 (m, 3H), 3.71-3.21 (m, 4H), 2.64-2.54 (m, 3H), 2.50-2.31 (m, 2H), 2.20-1.95 (m, 5H), 1.92-1.69 (m, 4H), 1.66-1.23 (m, 8H), 0.99-0.85 (m, 5H), 0.82-0.74 (m, 1H), 0.69-0.61 (m, 1H); LCMS (ESI, <i>m/z</i>): [M-H] ⁻ 781.3
27	 1-((<i>R</i>)-1-(3,3-difluorocyclobutyl)ethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (m, 1H), 8.67 (d, <i>J</i> = 8.0 Hz, 1H), 8.08-7.96 (m, 1H), 7.79-7.68 (m, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.13 (m, 2H), 6.92 (d, <i>J</i> = 2.0 Hz, 1H), 6.04-5.60 (m, 1H), 5.24-5.16 (m, 2H), 4.67-4.63 (m, 1H), 4.36 (m, 1H), 3.88 (m, 1H), 3.00-2.90 (m, 1H), 2.72-2.55 (m, 2H), 2.39-2.22 (m, 3H), 2.20-1.94 (m, 7H), 1.92-1.03 (m, 13H), 1.00-0.58 (m, 7H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 785.4.
28	 1-((<i>R</i>)-1-(3,3-difluorocyclobutyl)ethyl)-<i>N</i>-((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.67 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.73 (t, <i>J</i> = 8.4 Hz, 1H), 7.55 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 6.95 (d, <i>J</i> = 2.0 Hz, 1H), 6.12-5.96 (m, 1H), 5.35-5.30 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.66 (t, <i>J</i> = 8.4 Hz, 1H), 3.48-3.32 (m, 4H), 2.75-2.59 (m, 4H), 2.43-2.36 (m, 2H), 2.42-2.25 (m, 4H), 2.22-1.94 (m, 6H), 1.92-1.64 (m, 4H), 1.60-1.42 (m, 2H), 1.38-1.28 (d, <i>J</i> = 6.4 Hz, 3H), 1.10-0.91 (m, 4H), 0.89-0.82 (m, 1H), 0.80-0.72 (m, 1H), 0.64-0.58 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 800.5.

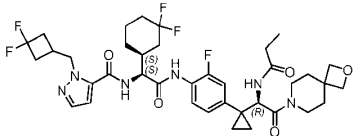
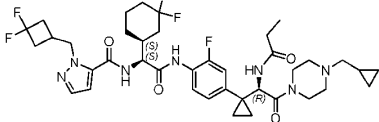
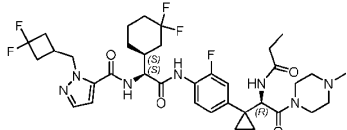
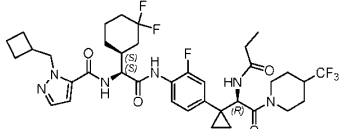
29	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.11 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.54-4.43 (m, 3H), 3.48-3.32 (m, 4H), 2.20-2.08 (m, 8H), 2.00-1.91 (m, 1H), 1.83-1.62 (m, 6H), 1.31-1.24 (t, <i>J</i> = 6.4 Hz, 3H), 1.22-0.71 (m, 13H), 0.62-0.55 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 638.3.
30	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.62 (d, <i>J</i> = 8.4 Hz, 1H), 7.99 (d, <i>J</i> = 8.8 Hz, 1H), 7.71 (t, <i>J</i> = 8.4 Hz, 1H), 7.59 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.11 (m, 3H), 6.44-6.16 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.96 (t, <i>J</i> = 14.4 Hz, 2H), 4.55 (t, <i>J</i> = 8.2 Hz, 1H), 3.45-3.31 (m, 4H), 2.33-2.13 (m, 8H), 2.00-1.92 (m, 1H), 1.83-1.62 (m, 5H), 1.32-0.66 (m, 14H), 0.65-0.59 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 674.4.
31	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (s, 1H), 8.50 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.53 (t, <i>J</i> = 8.4 Hz, 1H), 4.33 (d, <i>J</i> = 7.2 Hz, 2H), 3.48-3.28 (m, 4H), 2.22-2.05 (m, 8H), 1.99-1.91 (m, 1H), 1.88-1.60 (m, 5H), 1.35-1.15 (m, 3H), 1.12-0.75 (m, 12H), 0.62-0.56 (m, 1H), 0.41-0.37 (m, 2H), 0.32-0.28 (m, 2H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 664.4.
32	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.50 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.10 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.26-5.93 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.51 (t, <i>J</i> = 8.4 Hz, 1H), 4.33 (d, <i>J</i> = 7.1 Hz, 2H), 3.48-3.31 (m, 4H), 2.75-2.62 (m, 3H), 2.47-2.40 (m, 2H), 2.23-2.06 (m, 3H), 1.88-1.59 (m, 5H), 1.37-1.15 (m, 3H), 1.08-0.72 (m, 12H), 0.65-0.57 (m, 1H),

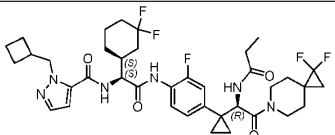
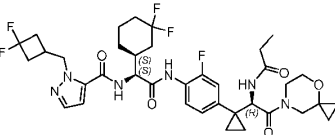
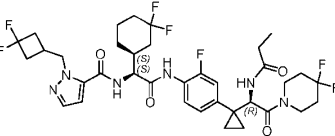
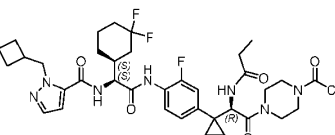
	methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	0.42-0.37 (m, 2H), 0.33-0.28 (m, 2H); LCMS (ESI, m/z): [M+H]⁺ 714.6.
33	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.90 (m, 1H), 8.63 (d, <i>J</i> = 8.0 Hz, 1H), 8.08-7.96 (m, 1H), 7.75-7.64 (m, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.11 (m, 3H), 6.48-6.15 (m, 1H), 6.05-5.75 (m, 1H), 5.24-5.15 (m, 1H), 5.01-4.88 (m, 2H), 4.55 (t, <i>J</i> = 8.4 Hz, 1H), 4.36 (m, 1H), 3.88 (m, 1H), 2.95 (m, 1H), 2.54-2.50 (m, 1H), 2.18-1.90 (m, 3H), 1.88-1.52 (m, 7H), 1.42-0.59 (m, 17H), LCMS (ESI, m/z): [M+H]⁺ 709.4.
34	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(2-fluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.87 (m, 1H), 8.53 (d, <i>J</i> = 8.4 Hz, 1H), 8.01-7.95 (m, 1H), 7.76-7.65 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.08 (m, 3H), 5.90-5.75 (m, 1H), 5.24-5.15 (m, 1H), 4.83-4.76 (m, 3H), 4.67-4.66 (m, 1H), 4.52 (t, <i>J</i> = 7.6 Hz, 1H), 4.39-4.36 (m, 1H), 3.89 (t, <i>J</i> = 12.0 Hz, 1H), 2.99-2.92 (m, 1H), 2.55-2.50 (m, 1H), 2.20-1.92 (m, 3H), 1.92-1.58 (m, 7H), 1.28-0.62 (m, 17H), LCMS (ESI, m/z): [M+H]⁺ 691.5.
35	 1-cyclopropyl-<i>N</i>-((<i>R</i>)-1-(1-(4-((<i>S</i>)-2-(1-ethyl-1<i>H</i>-pyrazole-5-carboxamido)-2-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.88 (s, 1H), 8.51-8.44 (m, 2H), 7.73 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.40 (d, <i>J</i> = 2.0 Hz, 1H), 7.30-7.21 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.89 (d, <i>J</i> = 2.0 Hz, 1H), 5.36 (d, <i>J</i> = 8.4 Hz, 1H), 4.55-4.42 (m, 3H), 4.29-4.24 (m, 1H), 3.56-3.40 (m, 4H), 2.31-2.15 (m, 7H), 1.84-1.62 (m, 5H), 1.30-1.17 (m, 5H), 1.11-0.97 (m, 5H), 0.94-0.81 (m, 8H), 0.75-0.70 (m, 1H); LCMS (ESI, m/z): [M+H]⁺ 716.4.
36	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.89 (s, 1H), 8.62 (d, <i>J</i> = 8.4 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.70 (t, <i>J</i> = 8.2 Hz, 1H), 7.60 (d, <i>J</i> = 1.6 Hz, 1H), 7.20-7.12 (m, 3H), 6.46-6.17 (m, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 5.01-4.92 (m, 2H), 4.55 (t, <i>J</i> = 8.4 Hz, 1H), 3.58-3.38 (m, 4H), 2.20-2.06 (m, 2H), 1.87-1.59 (m, 5H), 1.38-1.18 (m, 4H), 1.17-1.02 (m, 3H),

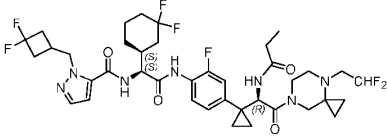
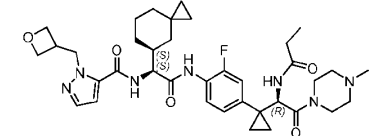
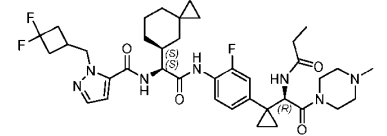
	yl)ethyl)cyclopropyl)phenyl)amino)-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	1.01-0.74 (m, 11H), 0.67-0.57 (m, 1H), 0.29 (s, 4H); LCMS (ESI, m/z): [M+H] ⁺ 685.4.
37	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(methyl-<i>d</i>₃)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.55 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.71 (t, <i>J</i> = 8.4 Hz, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 7.03 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.0 Hz, 1H), 4.59 (d, <i>J</i> = 6.0 Hz, 2H), 4.52 (t, <i>J</i> = 8.4 Hz, 1H), 3.48-3.35 (m, 4H), 2.63-2.53 (m, 3H), 2.47-2.30 (m, 3H), 2.25-2.05 (m, 5H), 1.99-1.91 (m, 1H), 1.87-1.60 (m, 5H), 1.34-1.14 (m, 2H), 1.11-0.73 (m, 11H), 0.64-0.57 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 717.4.
38	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.85 (m, 1H), 8.56-8.51 (m, 1H), 8.12-7.97 (m, 1H), 7.86-7.64 (m, 1H), 7.52 (d, <i>J</i> = 1.6 Hz, 1H), 7.22-7.13 (m, 2H), 7.30 (m, 1H), 5.24-5.12 (m, 1H), 4.62-4.47 (m, 3H), 4.42-4.37 (m, 1H), 3.91 (m, 1H), 3.02-2.92 (m, 1H), 2.61-2.35 (m, 6H), 2.20-2.03 (m, 2H), 1.88-1.59 (m, 7H), 1.39-1.02 (m, 4H), 1.00-0.53 (m, 12H); LCMS (ESI, m/z): [M+H] ⁺ 767.3.
39	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.56-8.53 (m, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.71-7.66 (m, 1H), 7.52 (d, <i>J</i> = 1.6 Hz, 1H), 7.22-7.13 (m, 2H), 7.04 (d, <i>J</i> = 1.6 Hz, 1H), 5.18 (d, <i>J</i> = 8.6 Hz, 1H), 4.62-4.60 (d, <i>J</i> = 5.6 Hz, 2H), 4.54-4.49 (m, 1H), 3.70-3.20 (m, 4H), 2.59-2.52 (m, 3H), 2.45-2.32 (m, 2H), 2.24-2.05 (m, 2H), 1.88-1.75 (m, 2H), 1.73-1.59 (m, 3H), 1.58-1.40 (m, 3H), 1.39-1.14 (m, 5H), 1.11-0.74 (m, 12H), 0.67-0.62 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 761.2.
40	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.87 (m, 1H), 8.64-8.58 (m, 1H), 8.12-7.97 (m, 1H), 7.86-7.65 (m, 1H), 7.61 (d, <i>J</i> = 1.6 Hz, 1H), 7.22-7.10 (m, 3H), 6.49-6.16 (m, 1H), 5.25-5.12 (m, 1H), 5.04-4.89 (m, 2H), 4.62-4.51 (m, 1H), 4.46-4.35 (m, 1H), 3.94-3.88 (m,

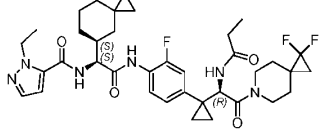
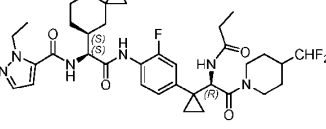
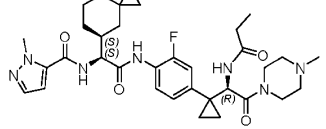
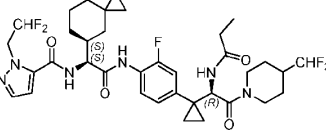
	1-(2,2-difluoroethyl)- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-1-((1 <i>r</i> ,4 <i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H, 3.03-2.96 (m, 1H), 2.60-2.55 (m, 1H), 2.22-2.04 (m, 2H), 1.86-1.58 (m, 7H), 1.42-1.14 (m, 4H), 1.14-0.53 (m, 14H), LCMS (ESI, m/z): [M+H] ⁺ 727.2.
41	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.85 (m, 1H), 8.56-8.51 (m, 1H), 8.12-7.96 (m, 1H), 7.85-7.65 (m, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.13 (m, 2H), 7.03 (m, 1H), 6.13-5.98 (m, 1H), 5.27-5.12 (m, 1H), 4.60-4.49 (m, 3H), 4.31-4.22 (m, 1H), 3.80-3.71 (m, 1H), 3.21-3.10 (m, 1H), 2.80-2.32 (m, 6H), 2.22-2.05 (m, 2H), 1.86-1.53 (m, 7H), 1.44-1.13 (m, 3H), 1.11-0.51 (m, 14H); LCMS (ESI, m/z): [M+H] ⁺ 783.4.
42	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)-4-hydroxypiperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.56-8.54 (m, 1H), 8.09-7.97 (m, 1H), 7.76-7.65 (m, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.04 (m, 1H), 5.82-5.43 (m, 1H), 5.37-5.32 (m, 1H), 5.23-5.17 (m, 1H), 4.62-4.56 (m, 2H), 4.52 (m, 1H), 4.25-4.21 (m, 1H), 3.73 (m, 1H), 3.22-3.12 (m, 1H), 2.82-2.70 (m, 1H), 2.64-2.53 (m, 2H), 2.49-2.31 (m, 2H), 2.23-2.04 (m, 2H), 1.85-1.77 (m, 2H), 1.71-1.62 (m, 3H), 1.56-1.41 (m, 2H), 1.40-1.15 (m, 3H), 1.13-1.00 (m, 2H), 0.98-0.93 (m, 4H), 0.90-0.82 (m, 6H), 0.80-0.72 (m, 1H), 0.67-0.55 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 765.4.
43	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.54-8.51 (m, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.72-7.64 (m, 1H), 7.50 (d, <i>J</i> = 1.6 Hz, 1H), 7.22-7.13 (m, 2H), 7.03 (d, <i>J</i> = 1.6 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.75 (d, <i>J</i> = 7.2 Hz, 2H), 4.62-4.46 (m, 3H), 4.41-4.35 (m, 2H), 3.72-3.20 (m, 5H), 2.23-2.04 (m, 2H), 1.88-1.40 (m, 8H), 1.38-1.14 (m, 5H), 1.12-0.75 (m, 12H), 0.69-0.57 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 727.6.

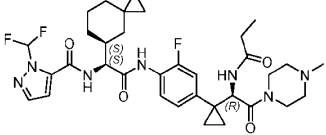
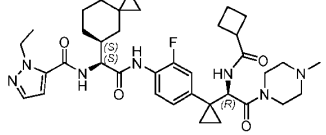
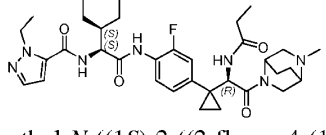
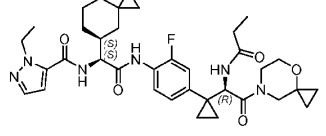
	(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide	
44	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (s, 1H), 8.45 (d, <i>J</i> = 5.6 Hz, 1H), 8.05 (d, <i>J</i> = 8.4 Hz, 1H), 7.73-7.66 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.13 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.17 (d, <i>J</i> = 8.0 Hz, 1H), 4.54-4.43(m, 3H), 3.67-3.22 (m, 4H), 2.21-2.05 (m, 2H), 1.83-1.47 (m, 8H), 1.43-1.17 (m, 8H), 1.12-0.77 (m, 12H), 0.67-0.60 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 685.4.
45	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (d, <i>J</i> = 8.4 Hz, 1H), 8.50 (d, <i>J</i> = 8.0 Hz, 1H), 8.07-7.97 (m, 1H), 7.72-7.64 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.06 (m, 2H), 6.98 (d, <i>J</i> = 2.0 Hz, 1H), 6.05-5.74 (m, 1H), 5.22-5.02 (m, 1H), 4.54-4.46 (m, 1H), 4.33 (d, <i>J</i> = 8.0 Hz, 2H), 3.71-3.38 (m, 2H), 3.31-2.90 (m, 4H), 2.82-2.54 (m, 2H), 2.22-2.05 (m, 2H), 1.86-1.57 (m, 5H), 1.42-1.14 (m, 4H), 1.12-1.00 (m, 2H), 0.99-0.70 (m, 10H), 0.67-0.43 (m, 4H), 0.41-0.28 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 740.9.
46	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-1-((1<i>r</i>,4<i>S</i>)-4-methylcyclohexyl)-2-oxoethyl)-1-(2,2,2-trifluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.72 (d, <i>J</i> = 6.4 Hz, 1H), 8.08-7.96 (m, 1H), 7.74-7.64 (m, 2H), 7.21-7.12 (m, 3H), 6.12-5.62 (m, 1H), 5.50-5.41 (m, 2H), 5.24-5.15 (m, 1H), 4.55 (t, <i>J</i> = 8.0 Hz, 1H), 4.40-4.31 (m, 1H), 3.89 (m, 1H), 3.01-2.87 (m, 1H), 2.62-2.55 (m, 1H), 2.22-1.90 (m, 3H), 1.88-1.58 (m, 7H), 1.32-0.59 (m, 17H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 727.3.
47	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96 (s, 1H), 8.62 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.67-7.60 (m, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.15 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 5.20-5.15 (m, 1H), 4.76-4.71 (m, 3H), 4.60-4.54 (m, 2H), 4.41-4.37 (m, 2H), 3.72-3.20 (m, 5H), 2.22-1.95 (m, 5H), 1.82-1.22 (m, 12H), 0.98-0.82 (m, 5H), 0.82-0.75

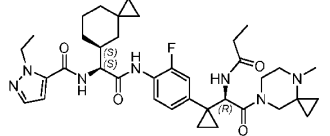
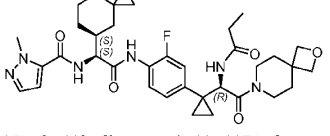
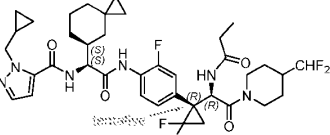
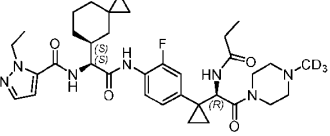
	difluorocyclohexyl)-2-oxoethyl)-1-(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide	(m, 1H), 0.69-0.62 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 749.4.
48	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.64 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.4 Hz, 1H), 7.66-7.62 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.06 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.4 Hz, 1H), 4.73 (t, <i>J</i> = 8.0 Hz, 1H), 4.61-4.59 (m, 2H), 4.28-4.22 (m, 4H), 3.30-3.20 (m, 4H), 2.59-2.38 (m, 5H), 2.22-1.96 (m, 5H), 1.84-1.56 (m, 7H), 1.47-1.32 (m, 2H), 1.29-1.22 (m, 1H), 0.99-0.92 (m, 4H), 0.87-0.72 (m, 2H), 0.62-0.58 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 763.8.
49	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(cyclopropylmethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.64 (d, <i>J</i> = 8.8 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 7.07 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.75 (t, <i>J</i> = 8.2 Hz, 1H), 4.60 (m, 2H), 3.44-3.32 (m, 4H), 2.59-2.50 (m, 3H), 2.46-2.32 (m, 4H), 2.22-1.93 (m, 9H), 1.84-1.62 (m, 4H), 1.41-1.32 (m, 1H), 1.28-1.20 (m, 1H), 1.00-0.93 (m, 4H), 0.87-0.72 (m, 3H), 0.48 (m, 1H), 0.43 (m, 2H), 0.06-0.01 (m, 2H); LCMS (ESI, m/z): [M+H] ⁺ 776.3.
50	 1-((3,3-difluorocyclobutyl)methyl)-<i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.64 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.08 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.75 (t, <i>J</i> = 8.0 Hz, 1H), 4.60 (d, <i>J</i> = 5.6 Hz, 2H), 3.53-3.35 (m, 4H), 2.66-2.31 (m, 5H), 2.29-1.92 (m, 12H), 1.86-1.61 (m, 4H), 1.46-1.33 (m, 1H), 1.30-1.18 (m, 1H), 1.06-0.92 (m, 4H), 0.90-0.73 (m, 2H), 0.65-0.56 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 736.8.
51	 1-(cyclobutylmethyl)-<i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (m, 1H), 8.60 (m, 1H), 8.12-7.98 (m, 1H), 7.83-7.64 (m, 1H), 7.48 (d, <i>J</i> = 1.2 Hz, 1H), 7.27-7.14 (m, 2H), 6.97 (d, <i>J</i> = 1.2 Hz, 1H), 5.27-5.13 (m, 1H), 4.77-4.71 (m, 1H), 4.51 (d, <i>J</i> = 6.8 Hz, 2H), 4.42-4.36 (m, 1H), 3.95-3.89

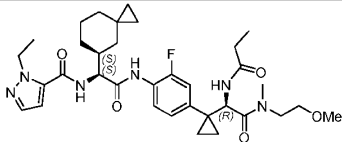
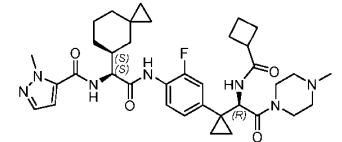
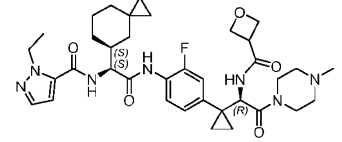
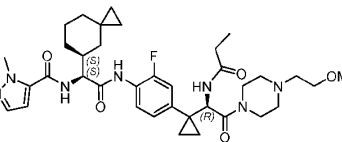
	4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenylamino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	(m, 1H), 3.03-2.94 (m, 1H), 2.70-2.55 (m, 3H), 2.22-1.90 (m, 5H), 2.09-1.60 (m, 12H), 1.48-0.52 (m, 11H); LCMS (ESI, m/z): [M+H] ⁺ 753.8.
52	 1-(cyclobutylmethyl)- <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.95 (s, 1H), 8.59 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.66 (dd, <i>J</i> = 12.0 Hz, 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 1.6 Hz, 1H), 7.22 (d, <i>J</i> = 12.0 Hz, 1H), 7.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.17 (m, 1H), 4.73 (t, <i>J</i> = 8.4 Hz, 1H), 4.51 (d, <i>J</i> = 7.2 Hz, 2H), 3.70-3.18 (m, 4H), 2.72-2.63 (m, 1H), 2.25-1.93 (m, 5H), 1.98-1.16 (m, 18H), 1.02-0.85 (m, 5H), 0.82-0.75 (m, 1H), 0.68-0.60 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 747.8.
53	 1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99-9.96 (m, 1H), 8.65 (d, <i>J</i> = 8.0 Hz, 1H), 8.08-8.00 (m, 1H), 7.66-7.58 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.06 (m, 3H), 5.25-5.08 (m, 1H), 4.81-4.70 (m, 1H), 4.60 (d, <i>J</i> = 6.0 Hz, 2H), 3.70-3.20 (m, 6H), 2.60-2.51 (m, 3H), 2.49-2.39 (m, 2H), 2.26-1.95 (m, 5H), 1.95-1.67 (m, 4H), 1.48-1.34 (m, 1H), 1.30-1.18 (m, 1H), 0.98-0.83 (m, 5H), 0.80-0.50 (m, 5H), 0.40-0.36 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 749.3.
54	 1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4,4-difluoropiperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.65 (d, <i>J</i> = 8.4 Hz, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.25-7.15 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 5.16 (d, <i>J</i> = 8.8 Hz, 1H), 4.75 (t, <i>J</i> = 8.0 Hz, 1H), 4.60 (d, <i>J</i> = 5.6 Hz, 2H), 3.72-3.54 (m, 1H), 3.41-3.32 (m, 2H), 2.60-2.31 (m, 8H), 2.22-1.60 (m, 12H), 1.00-0.91 (m, 4H), 0.88-0.82 (m, 1H), 0.80-0.72 (m, 1H), 0.68-0.61 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 757.3.
55	 1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4,4-difluoropiperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.64 (d, <i>J</i> = 8.0 Hz, 1H), 8.09 (t, <i>J</i> = 8.8 Hz, 1H), 7.68-7.62 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.25 (d, <i>J</i> = 11.6 Hz, 1H), 7.17 (d, <i>J</i> = 8.4 Hz, 1H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 6.85-

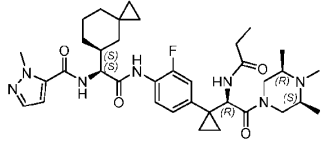
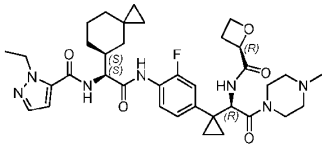
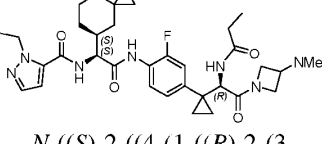
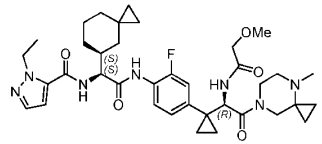
	<i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroacetyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide	6.58 (m, 1H), 5.14 (d, <i>J</i> = 8.4 Hz, 1H), 4.76 - 4.72 (t, <i>J</i> = 8.0 Hz, 1H), 4.61 (d, <i>J</i> = 6.0 Hz, 2H), 3.57-3.38 (m, 8H), 2.60-2.52 (m, 3H), 2.46-2.37 (m, 2H), 2.22-2.00 (m, 5H), 1.84-1.62 (m, 4H), 1.42-1.39 (m, 1H), 1.28-1.19 (m, 1H), 0.99-0.88 (m, 5H), 0.80-0.74 (m, 1H), 0.69-0.65 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 800.6.
56	 1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (m, 1H), 8.65 (d, <i>J</i> = 8.4 Hz, 1H), 8.08-7.98 (m, 1H), 7.70-7.61 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.07 (m, 3H), 6.14-5.71 (m, 1H), 5.25-5.05 (m, 1H), 4.74 (m, 1H), 4.60 (d, <i>J</i> = 6.0 Hz, 2H), 3.67-3.34 (m, 2H), 3.31-2.91 (m, 4H), 2.79-2.32 (m, 7H), 2.25-1.94 (m, 5H), 1.90-1.61 (m, 3H), 1.41 (m, 1H), 1.30-1.06 (m, 3H), 1.00-0.72 (m, 5H), 0.63-0.30 (m, 5H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 812.5.
57	 <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-(oxetan-3-ylmethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.51 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.50 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.12 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.4 Hz, 1H), 4.75 (d, <i>J</i> = 7.2 Hz, 2H), 4.58-4.54 (m, 3H), 4.40-4.36 (m, 2H), 3.49-3.31 (m, 5H), 2.26-1.92 (m, 10H), 1.74-1.66 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.39-1.28 (m, 1H), 1.24-1.13 (m, 1H), 1.02-0.91 (m, 5H), 0.89-0.73 (m, 3H), 0.65-0.58 (m, 1H), 0.28-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 692.4.
58	 1-((3,3-difluorocyclobutyl)methyl)- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.54 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.63-4.52 (m, 3H), 3.48-3.31 (m, 4H), 2.61-2.51 (m, 3H), 2.44-2.35 (m, 2H), 2.26-1.93 (m, 10H), 1.73-1.66 (m, 2H), 1.60 (m, 1H), 1.49 (m, 1H), 1.40-1.28 (m, 1H), 1.27-1.15 (m, 1H), 1.05-0.96 (m, 5H), 0.85-0.72 (m, 3H), 0.65-0.56 (m, 1H), 0.29-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 726.3.

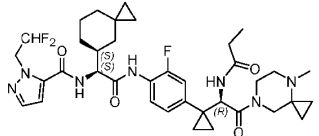
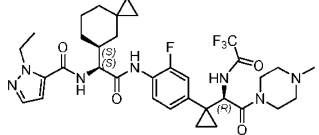
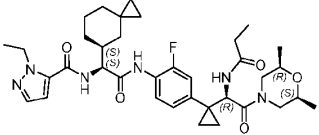
59	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 (d, <i>J</i> = 8.0 Hz, 1H), 8.05 (d, <i>J</i> = 8.4 Hz, 1H), 7.67-7.62 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.25-7.12 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.22-5.18 (m, 1H), 4.58-4.52 (m, 1H), 4.46 (t, <i>J</i> = 7.2 Hz, 2H), 3.68-3.40 (m, 3H), 3.32-3.25 (m, 1H), 2.22-2.02 (m, 3H), 1.73-1.42 (m, 7H), 1.38-1.12 (m, 8H), 1.02-0.75 (m, 8H), 0.68-0.60 (m, 1H), 0.28-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [<i>M</i> + <i>H</i>] ⁺ 697.4.
60	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 8.08-7.96 (m, 1H), 7.72-7.62 (m, 1H), 7.47 (s, 1H), 7.22-7.13 (m, 2H), 6.97 (m, 1H), 6.05-6.62 (m, 1H), 5.24-5.15 (m, 1H), 4.57 (t, <i>J</i> = 8.4 Hz, 1H), 4.46 (q, <i>J</i> = 6.8 Hz, 2H), 4.40-4.32 (m, 1H), 3.89 (t, <i>J</i> = 9.2 Hz, 1H), 3.02-2.90 (m, 1H), 2.55-2.52 (m, 1H), 2.19-1.96 (m, 4H), 1.70-1.57 (m, 5H), 1.55-1.32 (m, 2H), 1.29-1.05 (m, 7H), 1.02-0.62 (m, 7H), 0.28-0.12 (m, 4H); LCMS (ESI, <i>m/z</i>): [<i>M</i> + <i>H</i>] ⁺ 685.4
61	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 7.01 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.58 (t, <i>J</i> = 8.8 Hz, 1H), 4.02 (s, 3H), 3.42-3.32 (m, 4H), 2.22-1.92 (m, 10H), 1.72-1.66 (m, 2H), 1.63-1.12 (m, 4H), 1.02-0.93 (m, 5H), 0.87-0.72 (m, 3H), 0.62-0.57 (m, 1H), 0.27-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [<i>M</i> + <i>H</i>] ⁺ 636.5.
62	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (m, 1H), 8.61 (d, <i>J</i> = 8.4 Hz, 1H), 8.07-7.96 (m, 1H), 7.71-7.59 (m, 2H), 7.21-7.10 (m, 3H), 6.44-6.15 (m, 1H), 6.04-5.75 (m, 1H), 5.21-5.15 (m, 1H), 5.00-4.88 (m, 2H), 4.58 (t, <i>J</i> = 8.8 Hz, 1H), 4.38-4.32 (m, 1H), 3.88 (t, <i>J</i> = 12.0 Hz, 1H), 3.01-2.88 (m, 1H), 2.55-2.52 (m, 1H), 2.20-1.94 (m, 4H), 1.71-1.42 (m, 6H), 1.38-1.03 (m, 4H), 1.01-0.57 (m, 9H), 0.30-0.14 (m, 4H); LCMS (ESI, <i>m/z</i>): [<i>M</i> + <i>H</i>] ⁺ 721.4.

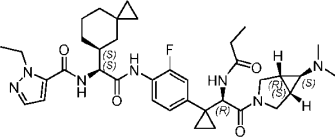
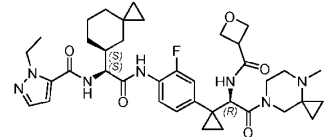
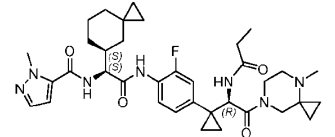
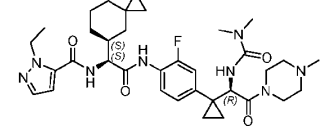
63	 1-(difluoromethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 8.87 (d, <i>J</i> = 8.4 Hz, 1H), 8.28 (t, <i>J</i> = 62.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.88 (s, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.32 (s, 1H), 7.19-7.12 (m, 2H), 5.19 (d, <i>J</i> = 9.2 Hz, 1H), 4.61 (t, <i>J</i> = 8.4 Hz, 1H), 3.46-3.35 (m, 4H), 2.25-1.92 (m, 10H), 1.76-1.66 (m, 2H), 1.64-1.47 (m, 2H), 1.41-1.17 (m, 2H), 1.02-0.90 (m, 5H), 0.88-0.72 (m, 3H), 0.60 (m, 1H), 0.30-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 672.4.
64	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-1-(cyclobutanecarboxamido)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.86 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.11 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.4 Hz, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.46-3.32 (m, 4H), 3.15 (m, 1H), 2.35-2.25 (m, 2H), 2.22-1.85 (m, 11H), 1.81-1.41 (m, 5H), 1.39-1.19 (m, 5H), 1.02-0.95 (m, 2H), 0.88-0.72 (m, 3H), 0.62-0.54 (m, 1H), 0.27-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 676.5.
65	 1-ethyl-<i>N</i>-((1<i>S</i>)-2-((2-fluoro-4-(1-((1<i>R</i>)-2-(5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR consists of a mixture of two diastereomers. LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 676.5.
66	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-oxa-7-azaspiro[2.5]octan-7-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.08-7.99 (m, 1H), 7.59-7.60 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.09 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.24-5.07 (m, 1H), 4.59-4.52 (m, 1H), 4.59-4.48 (m, 2H), 3.71-3.18 (m, 6H), 2.21-2.01 (m, 3H), 1.72-1.45 (m, 4H), 1.40-1.05 (m, 6H), 1.01-0.54 (m, 12H), 0.40-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 663.5.

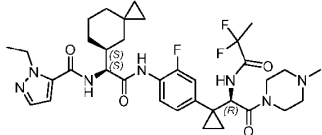
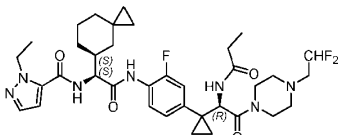
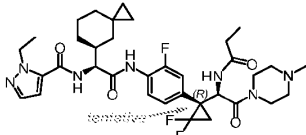
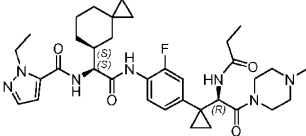
	2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	
67	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.05-7.96 (m, 1H), 7.71-7.65 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.08 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.24-5.08 (m, 1H), 4.61-4.53 (m, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.70-3.10 (m, 4H), 2.71-2.62 (m, 1H), 2.45-2.40 (m, 1H), 2.30-2.00 (m, 6H), 1.72-1.45 (m, 4H), 1.40-1.02 (m, 6H), 1.00-0.73 (m, 7H), 0.66-0.15 (m, 9H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 676.5.
68	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.64 (t, <i>J</i> = 8.0 Hz, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 7.01 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.4 Hz, 1H), 4.29-4.22 (m, 4H), 4.02 (s, 3H), 3.36-3.32 (m, 4H), 2.18-2.03 (m, 3H), 1.72-1.12 (m, 10H), 0.99-0.92 (m, 5H), 0.89-0.72 (m, 3H), 0.61 (m, 1H), 0.28-0.12 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 663.4.
69	 1-(cyclopropylmethyl)-<i>N</i>-((<i>S</i>)-2-((4-((<i>R</i>)-1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-2,2-difluorocyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.51 (d, <i>J</i> = 8.0 Hz, 1H), 8.36-8.22 (m, 1H), 7.77-7.71 (m, 1H), 7.47 (s, 1H), 7.36-7.27 (m, 1H), 7.15 (d, <i>J</i> = 8.0 Hz, 1H), 6.94 (s, 1H), 5.97-5.69 (m, 1H), 5.18-4.95 (m, 1H), 4.55 (t, <i>J</i> = 8.8 Hz, 1H), 4.40-4.24 (m, 3H), 3.76-3.63 (m, 1H), 3.02-2.90 (m, 1H), 2.55 (m, 1H), 2.21-1.92 (m, 5H), 1.88-1.45 (m, 7H), 1.40-0.80 (m, 10H), 0.40-0.18 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 747.7.
70	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(methyl-<i>d</i>₃)piperazin-1-yl)-2-oxo-1-propionamidoethyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.12 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.57 (t, <i>J</i> = 8.8 Hz, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.46-3.28 (m, 4H), 2.23-1.93 (m, 7H), 1.71-

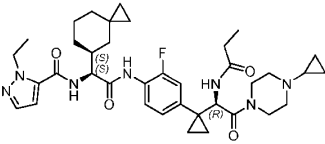
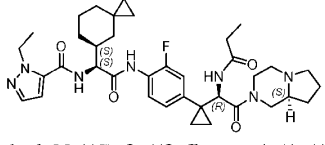
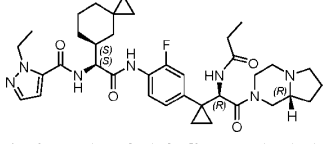
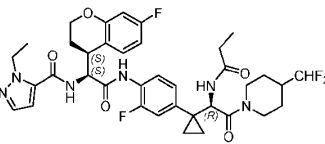
	oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	1.68 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.40-1.15 (m, 5H), 1.02-0.93 (m, 5H), 0.87-0.74 (m, 3H), 0.61 (m, 1H), 0.28-0.15 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 653.5.
71	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-((2-methoxyethyl)(methyl)amino)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR consists of a mixture of <i>cis</i> - and <i>trans</i> -amide conformers. LCMS (ESI, m/z): [M+H] ⁺ 639.5.
72	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-1-(cyclobutanecarboxamido)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 7.86 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.0 Hz, 1H), 7.45 (s, 1H), 7.17-7.10 (m, 2H), 7.02 (s, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.57 (t, <i>J</i> = 8.4 Hz, 1H), 4.02 (s, 3H), 3.45-3.35 (m, 4H), 3.15 (m, 1H), 2.25-2.15 (m, 2H), 2.17-1.80 (m, 11H), 1.77-1.65 (m, 3H), 1.60 (m, 1H), 1.49 (m, 1H), 1.35 (m, 1H), 1.20 (m, 1H), 1.02-0.91 (m, 2H), 0.89-0.72 (m, 3H), 0.61-0.56 (m, 1H), 0.30-0.15 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 662.5.
73	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-1-(oxetane-3-carboxamido)-2-oxoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.44 (d, <i>J</i> = 8.0 Hz, 1H), 8.17 (d, <i>J</i> = 8.4 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (m, 1H), 7.19-7.12 (m, 2H), 6.97 (m, 1H), 5.23 (d, <i>J</i> = 8.4 Hz, 1H), 4.63-4.52 (m, 4H), 4.48-4.43 (m, 3H), 3.86 (m, 1H), 3.45-3.28 (m, 4H), 2.22 (m, 2H), 2.12-2.03 (m, 6H), 1.73-1.65 (m, 2H), 1.62-1.42 (m, 2H), 1.40-1.10 (m, 5H), 0.99-0.92 (m, 2H), 0.88-0.72 (m, 3H), 0.65 (m, 1H), 0.30-0.12 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 678.5.
74	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(2-methoxyethyl)piperazin-1-yl)-2-oxo-ethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.42 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.67 (t, <i>J</i> = 8.0 Hz, 1H), 7.44 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 7.01 (d, <i>J</i> = 2.0 Hz, 1H), 5.17 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.8 Hz, 1H), 4.02 (s, 3H), 3.43-3.33 (m, 6H), 3.20 (s, 3H), 2.41 (t, <i>J</i> = 5.6 Hz, 2H),

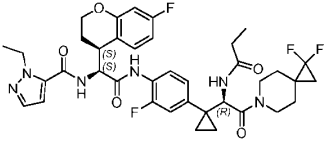
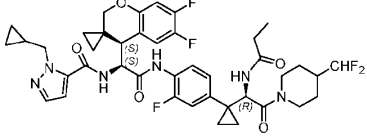
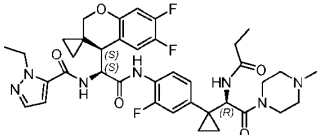
	1-propionamidoethyl)cyclopropyl-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide	2.37-2.29 (m, 2H), 2.22-2.01(m, 5H), 1.72-1.65 (m, 2H), 1.60 (m, 1H), 1.49 (m, 1H), 1.34 (m, 1H), 1.20 (m, 1H), 0.99-0.93 (m, 5H), 0.87-0.73 (m, 3H), 0.63-0.58 (m, 1H), 0.28-0.12 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 680.5.
75	 N-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-((3 <i>S</i> ,5 <i>R</i>)-3,4,5-trimethylpiperazin-1-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93-9.90 (m, 1H), 8.45-8.42 (m, 1H), 8.08-7.91 (m, 1H), 7.80-7.62 (m, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.11 (m, 2H), 7.02 (m, 1H), 5.27-5.11 (m, 1H), 4.61-4.52 (m, 1H), 4.14-4.07 (m, 1H), 4.00 (s, 3H), 3.65-3.45 (m, 1H), 2.71-2.55 (m, 1H), 2.32-1.83 (m, 8H), 1.72-1.45 (m, 4H), 1.42-1.11 (m, 4H), 1.02-0.72 (m, 13H), 0.65-0.48 (m, 1H), 0.30-0.15 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 664.5.
76	 1-ethyl- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-1-((<i>R</i>)-oxetane-2-carboxamido)-2-oxoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.74-7.69 (m, 2H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.15 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.07 (d, <i>J</i> = 8.8 Hz, 1H), 4.94-4.90 (m, 1H), 4.65-4.54 (m, 3H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.51-3.35 (m, 4H), 2.94 (m, 1H), 2.46-2.37 (m, 1H), 2.27-1.98 (m, 8H), 1.77-1.46 (m, 4H), 1.42-1.12 (m, 5H), 1.10-0.92 (m, 3H), 0.86-0.72 (m, 3H), 0.30-0.13 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 678.5.
77	 N-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(3-(dimethylamino)azetidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 7.97 (m, 1H), 7.74-7.64 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 4.61 (m, 1H), 4.56 (m, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 4.07-3.52 (m, 4H), 3.12-2.77 (m, 1H), 2.15-1.98 (m, 9H), 1.72-1.65 (m, 2H), 1.58 (m, 1H), 1.49 (m, 1H), 1.37-1.20 (m, 5H), 0.99-0.91 (m, 6H), 0.87-0.78 (m, 1H), 0.73-0.64 (m, 2H), 0.28-0.14 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 650.3.
78	 N-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(3-(dimethylamino)azetidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (m, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 7.72-7.55 (m, 2H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.06 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.15-5.02 (m, 1H), 4.60-4.53 (m, 1H), 4.50-4.42 (m, 2H),

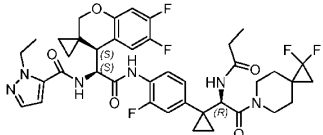
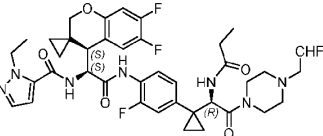
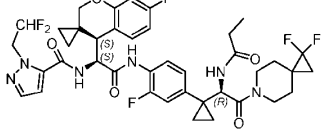
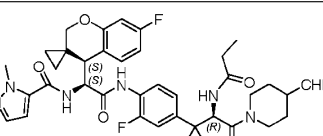
	1-ethyl- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-1-(2-methoxyacetamido)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxoethyl)cyclopropyl)phenyl)-amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 3.91-3.80 (m, 2H), 3.71-3.13 (m, 7H), 2.72-2.53 (m, 2H), 2.28-2.25 (m, 3H), 2.10-1.99 (m, 1H), 1.75-1.48 (m, 4H), 1.40-1.13 (m, 5H), 1.12-0.93 (m, 3H), 0.88-0.69 (m, 3H), 0.63-0.12 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 692.5.
79	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.61 (d, <i>J</i> = 8.4 Hz, 1H), 8.05-7.96 (m, 1H), 7.71-7.59 (m, 2H), 7.18-7.06 (m, 3H), 6.44-6.16 (m, 1H), 5.25-5.07 (m, 1H), 5.02-4.88 (m, 2H), 4.62-4.55 (m, 1H), 3.70-3.08 (m, 4H), 2.72-2.38 (m, 3H), 2.31-2.01 (m, 6H), 1.72-1.44 (m, 4H), 1.42-1.14 (m, 2H), 1.12-0.70 (m, 8H), 0.66-0.34 (m, 4H), 0.30-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 712.4.
80	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-(2,2,2-trifluoroacetamido)ethyl)-cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 9.61 (br, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.29-7.25 (m, 1H), 7.20-7.17 (m, 1H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (br, 1H), 4.56 (t, <i>J</i> = 8.4 Hz, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.55-3.33 (m, 4H), 2.26-2.16 (m, 7H), 2.08-2.04 (m, 1H), 1.73-1.65 (m, 2H), 1.60 (m, 1H), 1.49 (m, 1H), 1.39-1.16 (m, 5H), 1.04-0.96 (m, 3H), 0.85-0.79 (m, 3H), 0.28-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 690.4.
81	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-((2<i>S</i>,6<i>R</i>)-2,6-dimethylmorpholino)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (m, 1H), 8.45 (d, <i>J</i> = 8.0 Hz, 1H), 8.09-7.93 (m, 1H), 7.72-7.62 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.10 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.23-5.11 (m, 1H), 4.51 (t, <i>J</i> = 8.4 Hz, 1H), 4.46 (t, <i>J</i> = 7.2 Hz, 2H), 4.17 (d, <i>J</i> = 12.8 Hz, 1H), 3.73-3.42 (m, 1H), 3.39-3.20 (m, 2H), 2.77-2.56 (m, 2H), 2.22-1.99 (m, 3H), 1.72-1.45 (m, 4H), 1.40-1.14 (m, 5H), 1.11-0.72 (m, 13H), 0.64-0.51 (m, 1H), 0.28-0.14 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 665.4.

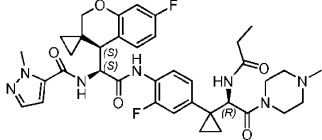
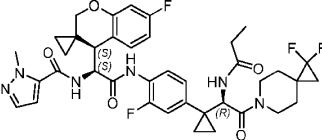
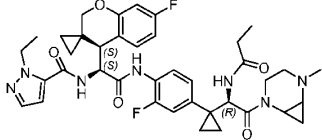
82	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-((1<i>R</i>,5<i>S</i>,6<i>S</i>)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.45 (m, 1H), 8.04-7.92 (m, 1H), 7.85-7.62 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.11 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 4.92-4.78 (m, 1H), 4.61-4.52 (m, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.63-3.35 (m, 3H), 3.25-2.18 (m, 1H), 2.20-2.02 (m, 9H), 1.71-1.46 (m, 6H), 1.42-1.18 (m, 5H), 1.01-0.90 (m, 5H), 0.85-0.56 (m, 5H), 0.28-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 676.5.
83	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-1-(oxetane-3-carboxamido)-2-oxoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 8.22-8.14 (m, 1H), 7.70-7.62 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.08 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.28-5.12 (m, 1H), 4.65-4.52 (m, 4H), 4.48-4.38 (m, 3H), 3.92-3.85 (m, 1H), 3.70-3.15 (m, 5H), 2.72-2.60 (m, 1H), 2.27-2.22 (m, 3H), 2.10-1.92 (m, 1H), 1.72-1.45 (m, 4H), 1.40-1.12 (m, 6H), 1.08-0.71 (m, 5H), 0.69-0.32 (m, 4H), 0.38-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 704.4.
84	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.42 (d, <i>J</i> = 8.4 Hz, 1H), 8.05-7.96 (m, 1H), 7.70-7.62 (m, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.07 (m, 2H), 7.02 (d, <i>J</i> = 2.0 Hz, 1H), 5.23-5.08 (m, 1H), 4.60-4.52 (m, 1H), 4.02 (s, 3H), 3.68-3.08 (m, 4H), 2.72-2.59 (m, 1H), 2.48-2.41 (m, 1H), 2.33-1.99 (m, 6H), 1.75-1.45 (m, 4H), 1.42-1.12 (m, 2H), 1.12-0.71 (m, 8H), 0.64-0.34 (m, 4H), 0.32-0.13 (m, 5H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 662.4.
85	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-1-(3,3-dimethylureido)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.85 (d, <i>J</i> = 8.8 Hz, 1H), 4.99 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.8 Hz, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.45-3.33 (m, 4H), 2.80 (s, 6H), 2.28-2.20 (m, 2H), 2.18-2.03 (m, 6H), 1.75-1.67 (m, 2H), 1.64-1.56 (m, 1H), 1.54-1.47 (m, 1H), 1.40-1.15 (m, 5H), 1.02-0.90 (m, 3H), 0.88-0.82 (m, 1H), 0.77-0.70 (m, 1H), 0.67-0.61

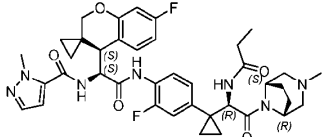
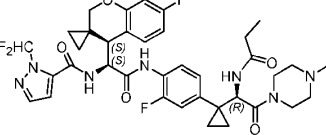
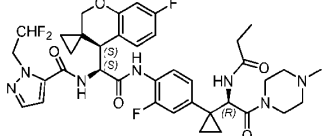
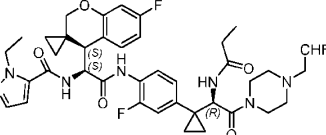
		(m, 1H), 0.39-0.16 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 665.5.
86	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-1-(2,2-difluoropropanamido)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.49-8.37 (m, 2H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.23 (d, <i>J</i> = 12.0 Hz, 1H), 7.16 (d, <i>J</i> = 8.4 Hz, 1H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.11 (d, <i>J</i> = 8.4 Hz, 1H), 4.54 (t, <i>J</i> = 8.4 Hz, 1H), 4.47 (q, <i>J</i> = 7.2 Hz, 2H), 3.50-3.33 (m, 4H), 2.31-2.19 (m, 4H), 2.16 (s, 3H), 2.12-1.98 (m, 1H), 1.79-1.66 (m, 5H), 1.63-1.44 (m, 2H), 1.40-1.14 (m, 5H), 1.08-0.94 (m, 3H), 0.87-0.72 (m, 3H), 0.30-0.13 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 686.5.
87	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.65 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 6.24-5.95 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.65 (t, <i>J</i> = 8.4 Hz, 1H), 3.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.50-3.25 (m, 4H), 2.75-2.62 (m, 2H), 2.45-2.25 (m, 3H), 2.22-1.98 (m, 4H), 1.75-1.43 (m, 4H), 1.42-1.15 (m, 5H), 1.05-0.90 (m, 5H), 0.88-0.70 (m, 3H), 0.62-0.56 (m, 1H), 0.38-0.14 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 700.5.
88	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2,2-difluoro-1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.46 (d, <i>J</i> = 8.0 Hz, 1H), 8.27 (d, <i>J</i> = 8.4 Hz, 1H), 7.76 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (s, 1H), 7.31 (d, <i>J</i> = 12.0 Hz, 1H), 7.15 (d, <i>J</i> = 7.6 Hz, 1H), 6.96 (s, 1H), 5.08 (d, <i>J</i> = 8.4 Hz, 1H), 4.57 (t, <i>J</i> = 8.0 Hz, 1H), 4.50-4.43 (m, 2H), 3.45-3.20 (m, 4H), 2.22-2.07 (m, 11H), 1.82-1.45 (m, 5H), 1.42-1.15 (m, 5H), 1.02-0.98 (m, 4H), 0.86-0.83 (m, 1H), 0.30-0.14 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 686.5.
89	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-ethylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.44 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.0 Hz, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.48-3.25 (m, 4H), 2.30-1.91 (m, 9H), 1.72-1.42 (m, 4H), 1.39-1.12 (m, 5H), 1.01-0.91 (m, 4H).

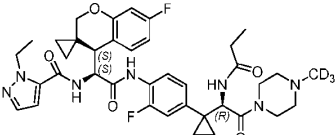
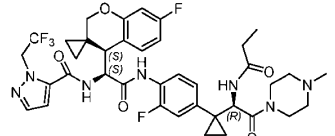
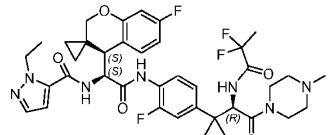
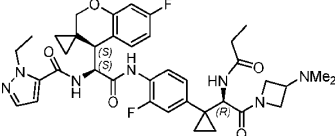
	fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	(m, 8H), 0.86-0.72 (m, 3H), 0.62-0.54 (m, 1H), 0.30-0.15 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 664.5.
90	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-cyclopropylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.43 (d, <i>J</i> = 8.0 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.12 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.55 (t, <i>J</i> = 8.4 Hz, 1H), 4.45 (q, <i>J</i> = 7.2 Hz, 2H), 3.48-3.24 (m, 4H), 2.49-2.41 (m, 2H), 2.33-2.28 (m, 1H), 2.19-2.08 (m, 4H), 1.71-1.46 (m, 5H), 1.41-1.15 (m, 5H), 1.02-0.93 (m, 5H), 0.85-0.73 (m, 3H), 0.62-0.57 (m, 1H), 0.38-0.15 (m, 8H); LCMS (ESI, m/z): [M+H] ⁺ 676.3.
91	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-((<i>S</i>)-hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1<i>H</i>)-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (s, 1H), 8.44 (d, <i>J</i> = 8.0 Hz, 1H), 8.11-7.93 (m, 1H), 7.74-7.61 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.08 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.30-5.14 (m, 1H), 4.60-4.56 (m, 1H), 4.50-4.22 (m, 3H), 3.91-3.67 (m, 1H), 3.07-2.77 (m, 3H), 2.62-2.53 (m, 2H), 2.28-1.84 (m, 5H), 1.80-1.43 (m, 8H), 1.40-1.05 (m, 6H), 1.01-0.54 (m, 8H), 0.35-0.11 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 676.5.
92	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-((<i>R</i>)-hexahydropyrrolo[1,2-<i>a</i>]pyrazin-2(1<i>H</i>)-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.90 (m, 1H), 8.46-8.43 (m, 1H), 8.06-7.91 (m, 1H), 7.79-7.62 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.14 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.32-5.16 (m, 1H), 4.60-4.25 (m, 4H), 3.82-3.70 (m, 1H), 3.00-2.82 (m, 3H), 2.65-2.60 (m, 2H), 2.30-1.85 (m, 5H), 1.80-1.46 (m, 8H), 1.43-1.10 (m, 6H), 1.08-0.47 (m, 8H), 0.30-0.12 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 676.5.
93	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.19 (m, 1H), 9.03 (d, <i>J</i> = 8.8 Hz, 1H), 8.11-7.97 (m, 1H), 7.70-7.58 (m, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.4 - 7.35 (m, 1H), 7.24-7.16 (m, 2H), 7.04-7.01 (m, 1H), 6.62-6.53 (m, 2H), 6.05-5.65 (m, 1H), 5.22-5.16 (m, 1H), 4.96 (m, 1H), 4.50 (m, 1H), 4.42-4.23 (m, 4H), 3.90

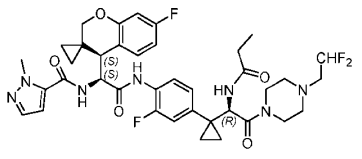
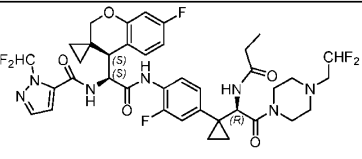
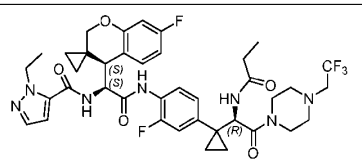
	oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorochroman-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	(m, 1H), 3.32-3.28 (m, 1H), 3.04-2.89 (m, 1H), 2.60-2.53 (m, 1H), 2.20-1.97 (m, 4H), 1.95-1.86 (m, 1H), 1.72-1.59 (m, 2H), 1.28-1.04 (m, 5H), 1.02-0.71 (m, 6H), 0.68-0.58 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 727.4.
94	 N-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorochroman-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.19 (s, 1H), 9.04 (d, <i>J</i> = 8.8 Hz, 1H), 8.09 (d, <i>J</i> = 8.8 Hz, 1H), 7.66-7.59 (m, 1H), 7.49 (d, <i>J</i> = 1.6 Hz, 1H), 7.37 (m, 1H), 7.25-7.17 (m, 2H), 7.03 (d, <i>J</i> = 1.6 Hz, 1H), 6.62-6.53 (m, 2H), 5.19-5.16 (m, 1H), 4.95 (m, 1H), 4.50 (m, 1H), 4.41-4.24 (m, 3H), 3.76-3.35 (m, 3H), 3.33-3.17 (m, 2H), 2.21-1.99 (m, 3H), 1.94-1.87 (m, 1H), 1.62-1.41 (m, 3H), 1.38-1.22 (m, 3H), 1.18 (t, <i>J</i> = 6.8 Hz, 3H), 1.02-0.85 (m, 5H), 0.84-0.76 (m, 1H), 0.72-0.62 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 739.3.
95	 1-(cyclopropylmethyl)-N-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)-piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.36 (m, 1H), 8.96 (m, 1H), 8.09-7.98 (m, 1H), 7.68-7.61 (m, 1H), 7.50 (d, <i>J</i> = 2.0 Hz, 1H), 7.35 (m, 1H), 7.24-7.16 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.88-6.83 (m, 1H), 6.04-5.64 (m, 1H), 5.25-5.02 (m, 3H), 4.40-4.27 (m, 3H), 4.21-4.13 (m, 2H), 3.89 (m, 1H), 3.43-3.33 (m, 1H), 3.03-2.88 (m, 1H), 2.53-2.49 (m, 1H), 2.23-1.92 (m, 3H), 1.69-1.60 (m, 2H), 1.25-0.72 (m, 10H), 0.68-0.59 (m, 2H), 0.56-0.49 (m, 1H), 0.33-0.13 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 797.6.
96	 N-((<i>S</i>)-1-((<i>S</i>)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 1H), 8.90 (m, 1H), 8.02 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.32 (m, 1H), 7.22-7.17 (m, 2H), 6.98 (d, <i>J</i> = 2.0 Hz, 1H), 6.85 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 5.14 (t, <i>J</i> = 10.0 Hz, 1H), 5.03 (d, <i>J</i> = 11.6 Hz, 1H), 4.42-4.25 (m, 2H), 3.44-3.32 (m, 5H), 2.55-2.51 (m, 1H), 2.26-1.95 (m, 9H), 1.45 (t, <i>J</i> = 6.8 Hz, 3H), 1.02-0.91 (m, 4H), 0.87-0.75 (m, 3H), 0.63-0.57 (m, 2H), 0.55-0.50 (m, 1H), 0.33-0.28 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 736.5.

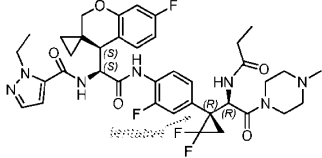
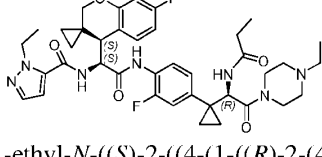
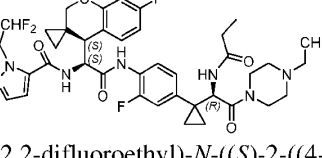
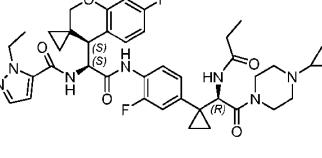
97	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.35 (s, 1H), 8.88 (d, <i>J</i> = 8.8 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.67 (q, <i>J</i> = 8.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.32 (m, 1H), 7.25-7.18 (m, 2H), 6.98 (d, <i>J</i> = 2.0 Hz, 1H), 6.86 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 5.14 (t, <i>J</i> = 9.6 Hz, 1H), 5.04 (d, <i>J</i> = 11.6 Hz, 1H), 4.40-4.27 (m, 2H), 3.71-3.20 (m, 5H), 2.55-2.52 (m, 1H), 2.21-2.07 (m, 2H), 1.64-1.25 (m, 6H), 1.15 (t, <i>J</i> = 7.6 Hz, 3H), 1.01-0.76 (m, 7H), 0.70-0.58 (m, 2H), 0.56-0.49 (m, 1H), 0.34-0.28 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 783.5.
98	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 1H), 8.90 (d, <i>J</i> = 9.2 Hz, 1H), 8.04 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.50 (d, <i>J</i> = 2.0 Hz, 1H), 7.38-7.27 (m, 1H), 7.26-7.15 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.89-6.82 (m, 1H), 6.25-5.96 (m, 1H), 5.19-5.12 (m, 2H), 5.05 (d, <i>J</i> = 11.2 Hz, 1H), 4.44-4.25 (m, 2H), 3.47-3.34 (m, 5H), 2.76-2.64 (m, 2H), 2.56-2.06 (m, 7H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H), 1.05-0.92 (m, 4H), 0.88-0.72 (m, 3H), 0.67-0.59 (m, 2H), 0.57-0.49 (m, 1H), 0.37-0.29 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 786.5.
99	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 9.08 (d, <i>J</i> = 8.8 Hz, 1H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (q, <i>J</i> = 8.4 Hz, 1H), 7.61 (d, <i>J</i> = 2.4 Hz, 1H), 7.30-7.16 (m, 4H), 6.61 (m, 1H), 6.49 (m, 1H), 6.23-5.92 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 5.14-5.04 (m, 2H), 4.88-4.75 (m, 2H), 3.70-3.20 (m, 5H), 2.56-2.52 (m, 1H), 2.19-2.09 (m, 2H), 1.53-1.22 (m, 6H), 0.97-0.85 (m, 5H), 0.83-0.73 (m, 2H), 0.70-0.48 (m, 3H), 0.33-0.24 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 801.5.
100	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-6,7-difluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.31 (m, 1H), 8.87 (d, <i>J</i> = 9.2 Hz, 1H), 8.08-7.97 (m, 1H), 7.75-7.65 (m, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.27 (m, 1H), 7.24-7.16 (m, 2H), 7.03 (m, 1H), 6.61 (m, 1H), 6.50 (m, 1H), 6.04-5.64 (m, 1H), 5.25-5.15 (m, 1H), 5.11-5.02 (m, 2H), 4.39-4.32 (m, 1H), 3.92-3.85 (m, 4H), 3.38-3.30 (m, 1H), 3.02-2.86 (m, 1H).

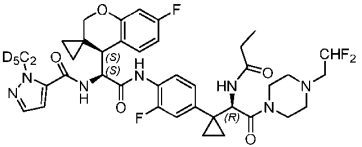
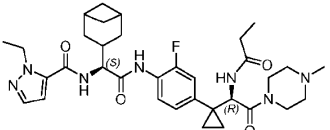
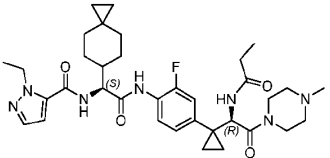
	propyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H), 2.60-2.50 (m, 2H), 2.20-1.95 (m, 3H), 1.70-1.58 (m, 2H), 1.30-1.00 (m, 2H), 0.98-0.72 (m, 7H), 0.68-0.54 (m, 2H), 0.52-0.48 (m, 1H), 0.30-0.25 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 739.5.
101	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.88 (d, <i>J</i> = 8.8 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.70 (t, <i>J</i> = 8.4 Hz, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.29 (m, 1H), 7.21-7.14 (m, 2H), 7.03 (d, <i>J</i> = 2.0 Hz, 1H), 6.61 (m, 1H), 6.50 (m, 1H), 5.20 (d, <i>J</i> = 9.2 Hz, 1H), 5.12-5.05 (m, 2H), 3.89 (s, 3H), 3.42-3.30 (m, 5H), 2.55-2.50 (m, 1H), 2.22-1.98 (m, 9H), 1.00-0.93 (m, 4H), 0.89-0.75 (m, 3H), 0.65-0.57 (m, 2H), 0.54-0.48 (m, 1H), 0.32-0.25 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 704.5.
102	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.89 (d, <i>J</i> = 9.2 Hz, 1H), 8.07 (d, <i>J</i> = 8.8 Hz, 1H), 7.73-7.67 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.18 (m, 3H), 7.04 (d, <i>J</i> = 2.0 Hz, 1H), 6.63-6.59 (m, 1H), 6.53-6.46 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 5.11-5.06 (m, 2H), 3.89 (s, 3H), 3.71-3.19 (m, 5H), 2.57-2.52 (m, 1H), 2.22-2.05 (m, 2H), 1.67-1.42 (m, 3H), 1.38-1.21 (m, 3H), 1.02-0.88 (m, 5H), 0.84-0.76 (m, 2H), 0.71-0.48 (m, 3H), 0.32-0.25 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 751.4.
103	 1-ethyl-<i>N</i>-((1<i>S</i>)-2-((2-fluoro-4-(1-((1<i>R</i>)-2-(5-methyl-2,5-diazabicyclo[4.1.0]heptan-2-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR consists of a mixture of two isomers. LCMS (ESI, m/z): [M+H] ⁺ 730.5.

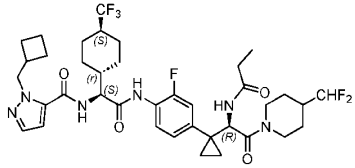
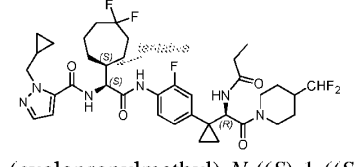
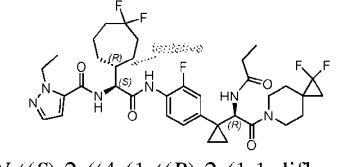
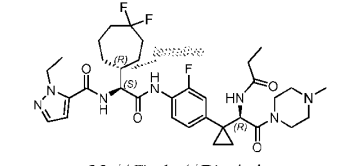
104	 <i>N</i>-((1<i>S</i>)-2-((2-fluoro-4-(1-((1<i>R</i>)-2-(3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.91 (m, 1H), 8.00 (m, 1H), 7.77-7.65 (m, 1H), 7.47 (m, 1H), 7.29 (m, 1H), 7.23-7.17 (m, 2H), 7.06-7.03 (m, 1H), 6.62 (m, 1H), 6.50 (m, 1H), 5.13-5.02 (m, 3H), 4.42-4.03 (m, 2H), 3.90 (m, 3H), 3.39-3.33 (m, 1H), 2.62-2.52 (m, 2H), 2.21-1.93 (m, 7H), 1.77-1.46 (m, 5H), 1.17-0.94 (m, 4H), 0.87-0.73 (m, 3H), 0.65-0.50 (m, 3H), 0.32-0.22 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 730.4.
105	 1-(difluoromethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.40 (s, 1H), 9.35 (d, <i>J</i> = 9.2 Hz, 1H), 8.17-7.88 (m, 3H), 7.72 (t, <i>J</i> = 8.4 Hz, 1H), 7.34 (s, 1H), 7.28-7.17 (m, 3H), 6.64-6.60 (m, 1H), 6.52-6.46 (m, 1H), 5.23-5.06 (m, 3H), 3.51-3.34 (m, 5H), 2.58-2.54 (m, 1H), 2.23-1.98 (m, 9H), 1.03-0.92 (m, 4H), 0.89-0.77 (m, 3H), 0.69-0.59 (m, 2H), 0.56-0.48 (m, 1H), 0.33-0.27 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 740.5.
106	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 1H), 9.08 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.70 (t, <i>J</i> = 8.4 Hz, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.31-7.71 (m, 4H), 6.63-6.59 (m, 1H), 6.51-6.46 (m, 1H), 6.24-5.94 (m, 1H), 5.20-5.01 (m, 3H), 4.88-4.72 (m, 2H), 3.45-3.28 (m, 5H), 2.58-2.54 (m, 1H), 2.31-1.90 (m, 9H), 1.03-0.77 (m, 7H), 0.69-0.58 (m, 2H), 0.56-0.48 (m, 1H), 0.35-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 754.4.
107	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.92 (d, <i>J</i> = 6.8 Hz, 1H), 8.04 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.16 (m, 3H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.63-6.59 (m, 1H), 6.53-6.48 (m, 1H), 6.25-5.95 (m, 1H), 5.18 (d, <i>J</i> = 8.4 Hz, 1H), 5.13-5.05 (m, 2H), 4.38-4.28 (m, 2H), 3.45-3.33 (m, 5H), 2.75-2.65 (m, 2H), 2.55-2.35 (m, 4H), 2.28-2.08 (m, 3H), 1.16

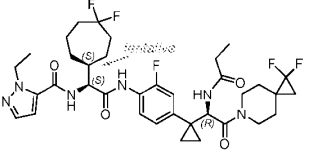
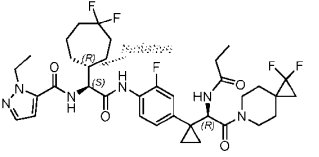
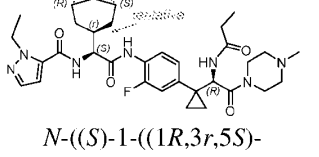
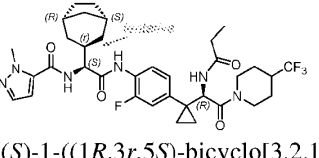
	fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	(t, <i>J</i> = 6.8 Hz, 3H), 1.02-0.95 (m, 4H), 0.89-0.75 (m, 3H), 0.68-0.58 (m, 2H), 0.56-0.49 (m, 1H), 0.31-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 768.5.
108	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(methyl-<i>d</i>3)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.91 (d, <i>J</i> = 9.6 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.27 (m, 1H), 7.22-7.16 (m, 2H), 6.98 (d, <i>J</i> = 2.0 Hz, 1H), 6.63-6.59 (m, 1H), 6.52-6.47 (m, 1H), 5.21 (d, <i>J</i> = 8.8 Hz, 1H), 5.13-5.05 (m, 2H), 4.42-4.24 (m, 2H), 3.48-3.32 (m, 5H), 2.56-2.53 (m, 1H), 2.25-1.98 (m, 6H), 1.15 (t, <i>J</i> = 7.2 Hz, 3H), 1.02-0.91 (m, 4H), 0.88-0.75 (m, 3H), 0.67-0.58 (m, 2H), 0.55-0.48 (m, 1H), 0.32-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 721.4.
109	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(2,2,2-trifluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 1H), 9.16 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.69-7.65 (m, 2H), 7.32-7.47 (m, 4H), 6.63-6.59 (m, 1H), 6.52-6.49 (m, 1H), 5.52-5.27 (m, 2H), 5.21 (d, <i>J</i> = 8.8 Hz, 1H), 5.14-5.05 (m, 2H), 3.48-3.35 (m, 5H), 2.59-2.52 (m, 1H), 2.22-2.18 (m, 8H), 2.06-1.95 (m, 1H), 1.03-0.91 (m, 4H), 0.89-0.76 (m, 3H), 0.68-0.59 (m, 2H), 0.56-0.49 (m, 1H), 0.33-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 772.4.
110	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-1-(2,2-difluoropropanamido)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.92 (d, <i>J</i> = 9.2 Hz, 1H), 8.45 (d, <i>J</i> = 8.4 Hz, 1H), 7.71 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (s, 1H), 7.41-7.18 (m, 3H), 6.99 (s, 1H), 6.65-6.57 (m, 1H), 6.53-6.47 (m, 1H), 5.16-5.05 (m, 3H), 4.40-4.28 (m, 2H), 3.52-3.36 (m, 5H), 2.59-2.52 (m, 1H), 2.31-2.20 (m, 4H), 2.17 (m, 3H), 1.74 (t, <i>J</i> = 19.2 Hz, 3H), 1.16 (t, <i>J</i> = 6.8 Hz, 3H), 1.09-0.95 (m, 2H), 0.85-0.74 (m, 3H), 0.67-0.48 (m, 2H), 0.33-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 754.4.
111	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-(dimethylamino)ethyl)-2-oxoethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (d, <i>J</i> = 5.6 Hz, 1H), 8.92 (d, <i>J</i> = 9.2 Hz, 1H), 8.00 (m, 1H), 7.75-7.67 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.31-7.17 (m, 3H), 6.99 (d, <i>J</i> = 2.0

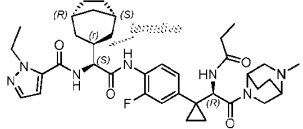
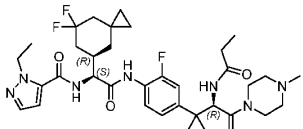
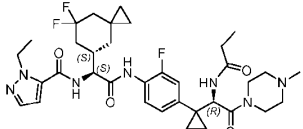
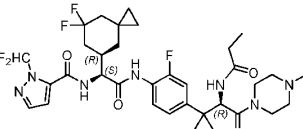
	<i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(3-(dimethylamino)azetidin-1-yl)-2-oxo-1-propionamidoethyl)cyclo-propyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H, 1H), 6.65-6.59 (m, 1H), 6.54-6.47 (m, 1H), 5.16-5.06 (m, 2H), 4.67-4.64 (m, 1H), 4.39-4.28 (m, 2H), 4.11-3.74 (m, 3H), 3.69-3.52 (m, 2H), 3.07-2.88 (m, 1H), 2.58-2.55 (m, 1H), 2.22-2.06 (m, 2H), 2.07-2.03 (m, 6H), 1.18 (t, <i>J</i> = 7.2 Hz, 3H), 1.02-0.89 (m, 5H), 0.85-0.69 (m, 3H), 0.65-0.59 (m, 1H), 0.56-0.49 (m, 1H), 0.33-0.26 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 718.4.
112	 <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 1H), 8.89 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.17 (m, 3H), 7.04 (d, <i>J</i> = 2.0 Hz, 1H), 6.62 (m, 1H), 6.50 (m, 1H), 6.24-5.96 (m, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 5.12-5.06 (m, 2H), 3.89 (s, 3H), 3.47-3.35 (m, 5H), 2.77-2.64 (m, 2H), 2.58-2.31 (m, 4H), 2.27-2.05 (m, 3H), 1.03-0.92 (m, 4H), 0.88-0.73 (m, 3H), 0.69-0.59 (m, 2H), 0.55-0.48 (m, 1H), 0.41-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 754.4.
113	 <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(difluoromethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.41 (s, 1H), 9.36 (d, <i>J</i> = 9.2 Hz, 1H), 8.18-7.88 (m, 3H), 7.72 (t, <i>J</i> = 8.0 Hz, 1H), 7.34 (s, 1H), 7.29-7.19 (m, 3H), 6.65-6.61 (m, 1H), 6.52-6.48 (m, 1H), 6.25-5.95 (m, 1H), 5.23-5.07 (m, 3H), 3.45-3.32 (m, 5H), 2.75-2.68 (m, 2H), 2.58-2.33 (m, 4H), 2.27-2.07 (m, 3H), 1.05-0.93 (m, 4H), 0.89-0.76 (m, 3H), 0.68-0.59 (m, 2H), 0.57-0.51 (m, 1H), 0.43-0.38 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 790.4.
114	 1-ethyl- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)ethyl)cyclopropyl)phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.91 (d, <i>J</i> = 9.2 Hz, 1H), 8.04 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (s, 1H), 7.32-7.18 (m, 3H), 6.99 (s, 1H), 6.63-6.60 (m, 1H), 6.53-6.48 (m, 1H), 5.20 (d, <i>J</i> = 8.4 Hz, 1H), 5.11-5.05 (m, 2H), 4.49-4.28 (m, 2H), 3.49-3.35 (m, 5H), 3.21-3.11 (m, 2H), 2.57-2.43 (m, 4H), 2.37-2.32 (m, 1H), 2.21-2.09 (m, 2H), 1.15 (t, <i>J</i> = 7.2 Hz, 3H), 1.03-0.77 (m, 7H), 0.69-0.58 (m, 2H), 0.57-

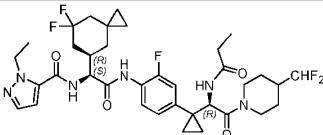
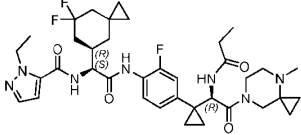
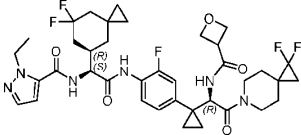
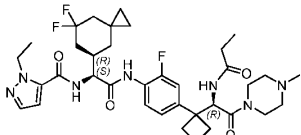
	cyclopropan]-4-yl)-2-oxoethyl)-1 <i>H</i> -pyrazole-5-carboxamide	0.49 (m, 1H), 0.32-0.26 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 786.5.
115	 <i>N</i>-((<i>S</i>)-2-((4-((<i>R</i>)-2,2-difluoro-1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.37 (s, 1H), 8.93 (d, <i>J</i> = 9.2 Hz, 1H), 8.30 (d, <i>J</i> = 8.8 Hz, 1H), 7.77 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.35-7.27 (m, 2H), 7.21 (d, <i>J</i> = 8.4 Hz, 1H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.63-6.60 (m, 1H), 6.53-6.50 (m, 1H), 5.14-5.07 (m, 3H), 4.38-4.28 (m, 2H), 3.39-3.19 (m, 5H), 2.56-2.52 (m, 1H), 2.25-2.03 (m, 10H), 1.88-1.76 (m, 1H), 1.15 (t, <i>J</i> = 7.2 Hz, 3H), 1.00 (t, <i>J</i> = 7.6 Hz, 3H), 0.82-0.77 (m, 1H), 0.65-0.48 (m, 2H), 0.38-0.25 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 754.4.
116	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((4-((<i>R</i>)-2-(4-ethylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.91 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.71 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.34-7.12 (m, 3H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 6.63-6.59 (m, 1H), 6.53-6.46 (m, 1H), 5.22 (d, <i>J</i> = 9.2 Hz, 1H), 5.15-5.06 (m, 2H), 4.47-4.25 (m, 2H), 3.49-3.32 (m, 5H), 2.61-2.52 (m, 1H), 2.31-2.01 (m, 8H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H), 1.04-0.90 (m, 7H), 0.88-0.77 (m, 3H), 0.68-0.59 (m, 2H), 0.54-0.48 (m, 1H), 0.32-0.25 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 732.5.
117	 1-(2,2-difluoroethyl)-<i>N</i>-((<i>S</i>)-2-((4-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.34 (s, 1H), 9.08 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.61 (d, <i>J</i> = 2.0 Hz, 1H), 7.31-7.17 (m, 4H), 6.63-6.59 (m, 1H), 6.51-6.46 (m, 1H), 6.25-5.89 (m, 2H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 5.14-5.05 (m, 2H), 4.89-4.75 (m, 2H), 3.45-3.35-3.28 (m, 5H), 2.78-2.67 (m, 2H), 2.58-2.05 (m, 7H), 1.04-0.92 (m, 4H), 0.88-0.75 (m, 3H), 0.69-0.58 (m, 2H), 0.57-0.48 (m, 1H), 0.35-0.26 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 804.4.
118	 1-ethyl-<i>N</i>-((<i>S</i>)-2-((4-((<i>R</i>)-2-(4-(1-ethyl-1<i>H</i>-pyrazol-5-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.90 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (s, 1H), 7.31-7.17 (m, 3H), 6.99 (s, 1H), 6.68-6.56 (m, 1H), 6.56-6.45 (m, 1H), 5.29 - 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 5.12-5.05 (m, 2H), 4.38-

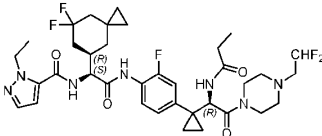
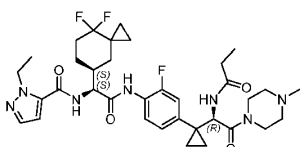
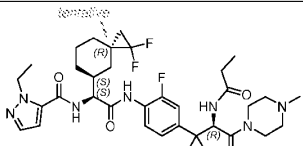
	<i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-cyclopropylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	4.24 (m, 2H), 3.45-3.22 (m, 5H), 2.55-2.30 (m, 4H), 2.22-2.05 (m, 3H), 1.60-1.50 (m, 1H), 1.16 (t, <i>J</i> = 7.2 Hz, 3H), 1.02-0.93 (m, 4H), 0.89-0.74 (m, 3H), 0.68-0.48 (m, 3H), 0.45-0.21 (m, 5H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 744.5.
119	 <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-(ethyl- <i>d</i> ₅)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.33 (s, 1H), 8.91 (d, <i>J</i> = 9.2 Hz, 1H), 8.04 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.32-7.16 (m, 3H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.64-6.58 (m, 1H), 6.52-6.47 (m, 1H), 6.27-5.94 (m, 1H), 5.24 - 5.17 (d, <i>J</i> = 8.8 Hz, 1H), 5.13-5.03 (m, 2H), 3.46-3.32 (m, 5H), 2.78-2.64 (m, 2H), 2.58-2.07 (m, 7H), 1.04-0.92 (m, 4H), 0.89-0.76 (m, 3H), 0.69-0.58 (m, 2H), 0.56-0.50 (m, 1H), 0.32-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 773.5.
120	 <i>N</i> -((<i>S</i>)-1-(bicyclo[3.1.1]heptan-3-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.53 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.74-7.69 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.68-4.62 (t, <i>J</i> = 8.4 Hz, 1H), 4.49 (q, <i>J</i> = 7.2 Hz, 2H), 3.54-3.38 (m, 4H), 2.71-2.64 (m, 1H), 2.42-1.95 (m, 13H), 1.91-1.79 (m, 2H), 1.73-1.65 (m, 1H), 1.60-1.41 (m, 2H), 1.32-1.20 (m, 3H), 1.03-0.92 (m, 5H), 0.90-0.72 (m, 2H), 0.65-0.58 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 636.4.
121	 1-ethyl- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-(spiro[2.5]octan-6-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91 (s, 1H), 8.49 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (d, <i>J</i> = 1.6 Hz, 1H), 7.21-7.10 (m, 2H), 7.00 (d, <i>J</i> = 1.6 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.59 (t, <i>J</i> = 8.4 Hz, 1H), 4.47 (q, <i>J</i> = 7.2 Hz, 2H), 3.45-3.28 (m, 4H), 2.27-2.04 (m, 8H), 1.99-1.73 (m, 3H), 1.70-1.58 (m, 3H), 1.41-1.19 (m, 5H), 1.04-0.99 (m, 6H), 0.98-0.81 (m, 1H), 0.80-0.72 (m, 1H), 0.64-0.55 (m, 1H), 0.29-0.21 (m, 2H), 0.20-0.13 (m, 2H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 650.5.

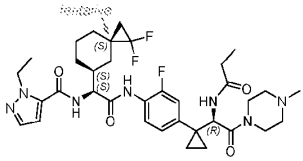
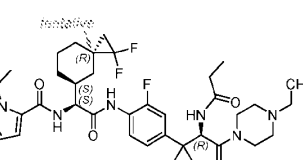
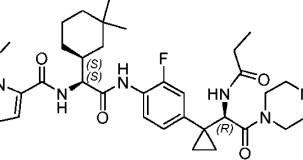
122	 1-(cyclobutylmethyl)-N-((S)-2-((4-((R)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((1r,4S)-4-(trifluoromethyl)cyclohexyl)ethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (m, 1H), 8.50 (m, 1H), 8.06-7.94 (m, 1H), 7.76-7.65 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.11 (m, 1H), 7.10 (m, 1H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 6.03-5.89 (m, 1H), 5.23-5.13 (m, 1H), 4.59-4.48 (m, 3H), 4.40-4.30 (m, 1H), 3.88 (t, <i>J</i> = 14.0 Hz, 1H), 3.02-2.86 (m, 1H), 2.70-2.62 (m, 1H), 2.48-2.42 (m, 1H), 2.30-2.00 (m, 3H), 1.96-1.56 (m, 13H), 1.32-1.05 (m, 6H), 0.95-0.51 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 767.6.
123	 1-(cyclopropylmethyl)-N-((S)-1-((S)-4,4-difluorocycloheptyl)-2-((4-((R)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (m, 1H), 8.58 (m, 1H), 8.08-7.96 (m, 1H), 7.76-7.65 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.13 (m, 2H), 6.98 (t, <i>J</i> = 2.0 Hz, 1H), 6.04 - 5.62 (m, 1H), 5.24-5.16 (m, 1H), 4.62 (m, 1H), 4.41-4.29 (m, 3H), 3.88 (m, 1H), 3.03-2.88 (m, 1H), 2.59-2.53 (m, 1H), 2.26-1.56 (m, 13H), 1.52-1.39 (m, 3H), 1.30-1.04 (m, 3H), 1.02-0.58 (m, 7H), 0.45-0.27 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 735.3.
124	 N-((S)-2-((4-((R)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((R)-4,4-difluorocycloheptyl)-2-oxoethyl)-1-ethyl-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.48 (m, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.74-7.66 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.12 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.68 (m, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.72-3.21 (m, 4H), 2.23-1.89 (m, 7H), 1.82 (m, 1H), 1.71-1.41 (m, 8H), 1.39-1.25 (m, 6H), 0.99-0.85 (m, 5H), 0.82-0.78 (m, 1H), 0.67-0.63 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 721.3.
125	 N-((S)-1-((R)-4,4-difluorocycloheptyl)-2-((2-fluoro-4-(1-((R)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (s, 1H), 8.48 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.0 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.13 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.68 (t, <i>J</i> = 8.0 Hz, 1H), 4.47 (t, <i>J</i> = 7.2 Hz, 2H), 3.46-3.25 (m, 4H), 2.26-1.90 (m, 14H), 1.87-1.76 (m, 1H), 1.73-1.62 (m, 2H), 1.57-1.48 (m, 3H), 1.28 (t, <i>J</i> = 7.2 Hz, 3H), 1.03-0.94 (m, 4H), 0.88-0.81 (m, 1H), 0.79-0.72 (m, 1H).

	oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	1H), 0.63-0.56 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 674.4.
126	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-4,4-difluorocycloheptyl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.52 (d, <i>J</i> = 7.2 Hz, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.74-7.67 (m, 1H), 7.48 (s, 1H), 7.23-7.14 (m, 2H), 6.99 (s, 1H), 5.17 (d, <i>J</i> = 8.4 Hz, 1H), 4.64 (m, 1H), 4.46 (q, <i>J</i> = 6.8 Hz, 2H), 3.69-3.25 (m, 4H), 2.28-1.85 (m, 7H), 1.81-1.22 (m, 15H), 1.03-0.56 (m, 7H); LCMS (ESI, m/z): [M+H] ⁺ 721.4.
127	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>R</i>)-4,4-difluorocycloheptyl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.95 (s, 1H), 8.65 (m, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.73-7.65 (m, 1H), 7.62 (s, 1H), 7.23-7.14 (m, 3H), 6.45-6.15 (m, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 5.04-4.88 (m, 2H), 4.73-4.65 (m, 1H), 3.70-3.20 (m, 4H), 2.25-1.89 (m, 7H), 1.85-1.23 (m, 12H), 1.01-0.85 (m, 5H), 0.81-0.77 (m, 1H), 0.68-0.61 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 757.4.
128	 <i>N</i>-((<i>S</i>)-1-((1<i>R</i>,3<i>r</i>,5<i>S</i>)-bicyclo[3.2.1]octan-3-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.86 (s, 1H), 8.46 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.11 (m, 2H), 6.97 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.50-4.43 (m, 3H), 3.47-3.28 (m, 4H), 2.22-2.03 (m, 11H), 1.98-1.91 (m, 1H), 1.67-1.44 (m, 4H), 1.42-1.32 (m, 4H), 1.29-1.24 (m, 4H), 1.13 (m, 1H), 1.02-0.92 (m, 4H), 0.86-0.80 (m, 1H), 0.79-0.73 (m, 1H), 0.63-0.57 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 650.5.
129	 <i>N</i>-((<i>S</i>)-1-((1<i>R</i>,3<i>r</i>,5<i>S</i>)-bicyclo[3.2.1]octan-3-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.91-9.82 (m, 1H), 8.48-8.43 (m, 1H), 8.13-7.98 (m, 1H), 7.82-7.62 (m, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.11 (m, 2H), 7.02 (m, 1H), 5.26-5.12 (m, 1H), 4.56-4.35 (m, 2H), 4.03 (m, 3H), 3.92 (m, 1H), 3.00 (m, 1H), 2.61-2.51 (m, 2H), 2.23-2.05 (m, 5H), 1.86-1.46 (m, 6H), 1.44-0.72 (m, 14H), 0.64-0.53 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 689.1.

	yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-methyl-1 <i>H</i> -pyrazole-5-carboxamide	
130	 <i>N</i>-((1<i>S</i>)-1-((1<i>R</i>,3<i>r</i>,5<i>S</i>)-bicyclo[3.2.1]octan-3-yl)-2-((2-fluoro-4-(1-((1<i>R</i>)-2-(5-methyl-2,5-diazabicyclo[2.2.2]octan-2-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR consists of a mixture of two isomers. LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 676.7.
131	 <i>N</i>-((<i>S</i>)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.00 (s, 1H), 8.58 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.22-7.15 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.0 Hz, 1H), 4.67 (t, <i>J</i> = 8.4 Hz, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.49-3.28 (m, 4H), 2.38 (m, 1H), 2.28-1.99 (m, 10H), 1.97-1.70 (m, 2H), 1.65 (m, 1H), 1.36 (m, 1H), 1.28 (t, <i>J</i> = 7.2 Hz, 3H), 1.05-0.92 (m, 5H), 0.89-0.73 (m, 2H), 0.63-0.57 (m, 1H), 0.43-0.31 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 686.8.
132	 <i>N</i>-((<i>S</i>)-1-((<i>S</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (s, 1H), 8.56 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.65 (t, <i>J</i> = 8.4 Hz, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 7.03 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.0 Hz, 1H), 4.75 (t, <i>J</i> = 8.0 Hz, 1H), 4.49-4.44 (q, <i>J</i> = 7.2 Hz, 2H), 3.47-3.25 (m, 4H), 2.42 (m, 1H), 2.22-2.05 (m, 10H), 2.01-1.72 (m, 3H), 1.39-1.22 (m, 4H), 1.03-0.91 (m, 4H), 0.89-0.73 (m, 3H), 0.64-0.58 (m, 1H), 0.43-0.22 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 686.4.
133	 1-(difluoromethyl)-<i>N</i>-((<i>S</i>)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.06 (s, 1H), 8.98 (d, <i>J</i> = 8.0 Hz, 1H), 8.26 (t, <i>J</i> = 58.8 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.85 (d, <i>J</i> = 1.6 Hz, 1H), 7.67 (t, <i>J</i> = 8.4 Hz, 1H), 7.31 (d, <i>J</i> = 1.6 Hz, 1H), 7.22-7.14 (m, 2H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.71 (t, <i>J</i> = 8.4 Hz, 1H), 3.53-3.26 (m, 4H), 2.47 (m, 1H), 2.28-

	methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	2.00 (m, 10H), 1.98-1.58 (m, 3H), 1.39-1.31 (m, 1H), 1.02-0.92 (m, 5H), 0.89-0.73 (m, 2H), 0.62-0.56 (m, 1H), 0.40-0.30 (m, 4H); LCMS (ESI, m/z): [M+H]⁺ 708.4.
134	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.99 (m, 1H), 8.57 (d, <i>J</i> = 8.4 Hz, 1H), 8.09-7.97 (m, 1H), 7.71-7.61 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.14 (m, 2H), 6.98 (d, <i>J</i> = 2.0 Hz, 1H), 6.07-5.62 (m, 1H), 5.22-5.15 (m, 1H), 4.66 (t, <i>J</i> = 8.0 Hz, 1H), 4.58-4.37 (m, 3H), 3.92-3.81 (m, 1H), 3.05-2.87 (m, 1H), 2.60-1.94 (m, 7H), 1.90-1.58 (m, 4H), 1.48 - 0.53 (m, 14H), 0.49-0.27 (m, 4H); LCMS (ESI, m/z): [M+H]⁺ 721.4.
135	 <i>N</i>-((<i>S</i>)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methyl-4,7-diazaspiro[2.5]octan-7-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.99 (m, 1H), 8.56 (d, <i>J</i> = 8.4 Hz, 1H), 8.05-7.96 (m, 1H), 7.70-7.62 (m, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.11 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.27-5.06 (m, 1H), 4.69-4.62 (m, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.69-3.05 (m, 4H), 2.70-2.32 (m, 3H), 2.25-1.98 (m, 7H), 1.89-1.59 (m, 3H), 1.40-1.22 (m, 4H), 1.11-0.72 (m, 7H), 0.66-0.19 (m, 9H); LCMS (ESI, m/z): [M+H]⁺ 712.5.
136	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-1-(oxetane-3-carboxamido)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.99 (s, 1H), 8.58-8.55 (m, 1H), 8.25-8.22 (m, 1H), 7.66-7.64 (m, 1H), 7.48 (s, 1H), 7.25-7.16 (m, 2H), 7.00 (s, 1H), 5.23 (t, <i>J</i> = 8.4 Hz, 1H), 4.66-4.44 (m, 7H), 3.90-3.86 (m, 1H), 3.70-3.23 (m, 4H), 2.52-2.34 (m, 1H), 2.28-2.21 (m, 1H), 2.19-2.00 (m, 1H), 1.88-1.42 (m, 5H), 1.38-1.26 (m, 7H), 1.01-0.65 (m, 5H), 0.39-0.31 (m, 4H); LCMS (ESI, m/z): [M+H]⁺ 761.4.
137		¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.01 (s, 1H), 8.58 (d, <i>J</i> = 8.0 Hz, 1H), 8.37 (d, <i>J</i> = 9.6 Hz, 1H), 7.79 (t, <i>J</i> = 8.0 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.12-7.07 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 4.99 (d, <i>J</i> = 9.6 Hz, 1H), 4.69 (t,

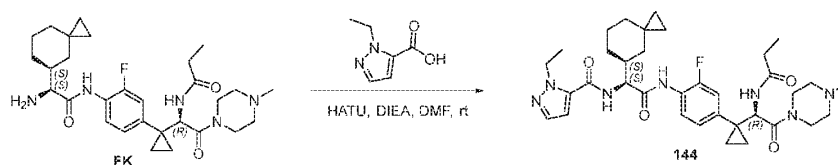
	<i>N</i> -((<i>S</i>)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclobutyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	$J = 8.4 \text{ Hz}$, 1H), 4.46 (q, $J = 7.2 \text{ Hz}$, 2H), 3.48-3.44 (m, 1H), 3.08-3.02 (m, 3H), 2.90-2.82 (m, 1H), 2.35-2.02 (m, 10H), 1.97 (s, 3H), 1.90-1.61 (m, 5H), 1.39-1.22 (m, 5H), 1.04-0.97 (m, 4H), 0.39-0.32 (m, 4H); LCMS (ESI, m/z): $[M+H]^+$ 700.4.
138	 <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclo-propyl)-2-fluorophenyl)amino)-1-((<i>R</i>)-7,7-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 8.57 (d, $J = 8.4 \text{ Hz}$, 1H), 8.03 (d, $J = 8.4 \text{ Hz}$, 1H), 7.65 (t, $J = 8.4 \text{ Hz}$, 1H), 7.48 (d, $J = 1.6 \text{ Hz}$, 1H), 7.23-7.14 (m, 2H), 7.00 (d, $J = 1.6 \text{ Hz}$, 1H), 6.25-5.94 (m, 1H), 5.18 (d, $J = 8.8 \text{ Hz}$, 1H), 4.65 (t, $J = 8.4 \text{ Hz}$, 1H), 4.47-4.42 (m, 2H), 3.48-3.36 (m, 4H), 2.78-2.60 (m, 2H), 2.42-1.97 (m, 9H), 1.92-1.60 (m, 2H), 1.40-1.16 (m, 4H), 1.08-0.56 (m, 8H), 0.42-0.20 (m, 4H); LCMS (ESI, m/z): $[M+H]^+$ 736.4.
139	 <i>N</i> -((<i>S</i>)-1-((<i>S</i>)-8,8-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 8.60 (d, $J = 8.0 \text{ Hz}$, 1H), 8.02 (d, $J = 8.8 \text{ Hz}$, 1H), 7.72 (t, $J = 8.4 \text{ Hz}$, 1H), 7.48 (d, $J = 2.0 \text{ Hz}$, 1H), 7.20-7.13 (m, 2H), 6.97 (d, $J = 2.0 \text{ Hz}$, 1H), 5.19 (d, $J = 8.8 \text{ Hz}$, 1H), 4.63 (t, $J = 8.4 \text{ Hz}$, 1H), 4.45 (q, $J = 7.2 \text{ Hz}$, 2H), 3.48-3.35 (m, 4H), 2.25-2.07 (m, 10H), 2.02-1.93 (m, 1H), 1.91-1.74 (m, 3H), 1.69-1.55 (m, 1H), 1.31-1.18 (m, 4H), 1.02-0.91 (m, 4H), 0.89-0.73 (m, 3H), 0.65-0.59 (m, 2H), 0.57-0.47 (m, 1H), 0.43-0.38 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 686.4.
140	 <i>N</i> -((<i>S</i>)-1-((3 <i>R</i> ,5 <i>S</i>)-1,1-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1 <i>H</i> -pyrazole-5-carboxamide	^1H NMR (400 MHz, DMSO- d_6) δ 9.97 (s, 1H), 8.48 (d, $J = 8.4 \text{ Hz}$, 1H), 8.00 (d, $J = 8.8 \text{ Hz}$, 1H), 7.68 (t, $J = 8.4 \text{ Hz}$, 1H), 7.48 (d, $J = 1.6 \text{ Hz}$, 1H), 7.19-7.12 (m, 2H), 6.95 (d, $J = 1.6 \text{ Hz}$, 1H), 5.19 (d, $J = 8.8 \text{ Hz}$, 1H), 4.60 (t, $J = 8.4 \text{ Hz}$, 1H), 4.45 (q, $J = 7.2 \text{ Hz}$, 2H), 3.45-3.33 (m, 4H), 2.23-1.92 (m, 10H), 1.72-1.67 (m, 2H), 1.61-1.51 (m, 1H), 1.44-1.21 (m, 10H), 1.02-0.93 (m, 4H), 0.87-0.82 (m, 1H), 0.79-0.72 (m, 1H), 0.62-0.57 (m, 1H); LCMS (ESI, m/z): $[M+H]^+$ 686.5.

141	 <i>N</i>-((<i>S</i>)-1-((3<i>S</i>,5<i>S</i>)-1,1-difluorospiro[2.5]octan-5-yl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.48 (d, <i>J</i> = 8.8 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.66 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.12 (m, 2H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.74 (t, <i>J</i> = 8.0 Hz, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.45-3.32 (m, 4H), 2.23-2.08 (m, 8H), 2.03-1.92 (m, 2H), 1.82-1.69 (m, 2H), 1.65-1.38 (m, 4H), 1.30-1.14 (m, 7H), 1.00-0.92 (m, 4H), 0.87-0.72 (m, 2H), 0.62-0.57 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 686.4.
142	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(4-(2,2-difluoroethyl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((3<i>R</i>,5<i>S</i>)-1,1-difluorospiro[2.5]octan-5-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 8.48 (d, <i>J</i> = 8.0 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.67 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.21-7.13 (m, 2H), 6.95 (d, <i>J</i> = 2.0 Hz, 1H), 6.25-5.95 (m, 1H), 5.19 (d, <i>J</i> = 8.0 Hz, 1H), 4.58 (t, <i>J</i> = 8.8 Hz, 1H), 4.46 (q, <i>J</i> = 7.2 Hz, 2H), 3.42-3.33 (m, 4H), 2.73-2.65 (m, 2H), 2.49-2.42 (m, 2H), 2.37-2.29 (m, 1H), 2.23-1.97 (m, 4H), 1.79-1.68 (m, 2H), 1.59-1.51 (m, 1H), 1.48-1.19 (m, 10H), 1.01-0.94 (m, 4H), 0.89-0.82 (m, 1H), 0.78-0.71 (m, 1H), 0.63-0.57 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 736.4.
143	 <i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-dimethylcyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)phenyl)amino)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.48 (d, <i>J</i> = 8.8 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.19-7.12 (m, 2H), 7.00 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 9.2 Hz, 1H), 4.55-4.44 (m, 3H), 3.45-3.28 (m, 4H), 2.25-2.02 (m, 9H), 1.99-1.92 (m, 1H), 1.68-1.24 (m, 8H), 1.09-0.74 (m, 15H), 0.64-0.58 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 652.5.

Example 144

1-ethyl-*N*-((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)-1*H*-pyrazole-5-carboxamide (144)

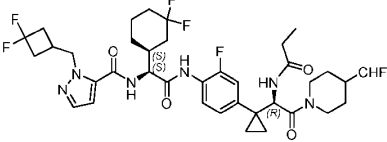
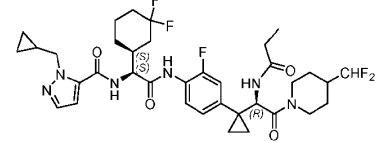
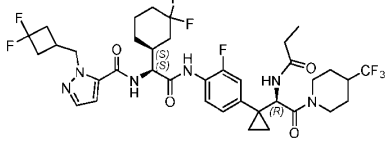
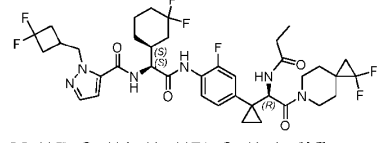
- 168 -

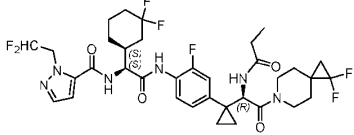
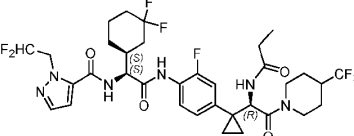
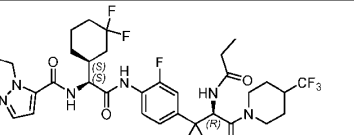
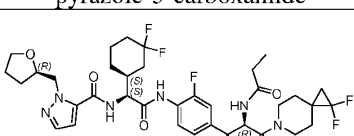


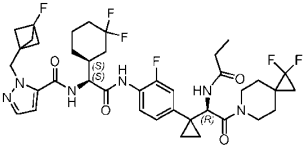
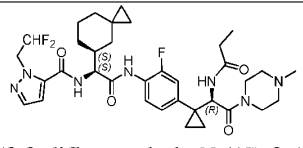
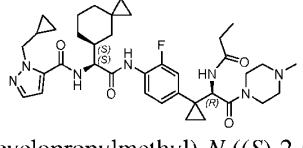
[0310] A solution of *N*-((*R*)-1-(1-(4-((*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (300 mg, 0.569 mmol), 1-ethyl-1*H*-pyrazole-5-carboxylic acid (80 mg, 0.57 mmol), HATU (324 mg, 0.853 mmol) and DIEA (220 mg, 1.71 mmol) in DMF (4 mL) was stirred at rt for 2 hrs. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (20:1), to afford impure product. The material was further purified by prep-HPLC (0.05% NH₄HCO₃) to afford Example **144**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.90 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.69 (t, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.19-7.11 (m, 2H), 6.97 (d, *J* = 2.0 Hz, 1H), 5.19 (d, *J* = 8.8 Hz, 1H), 4.56 (t, *J* = 8.4 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 3.48-3.32 (m, 4H), 2.22-1.94 (m, 10H), 1.72-1.46 (m, 4H), 1.41-1.10 (m, 5H), 1.02-0.93 (m, 5H), 0.87-0.74 (m, 3H), 0.63-0.59 (m, 1H), 0.28-0.15 (m, 4H); LCMS (ESI, *m/z*): [M+H]⁺ 650.4.

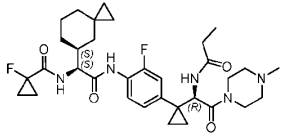
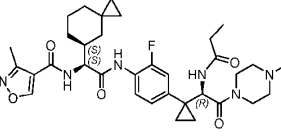
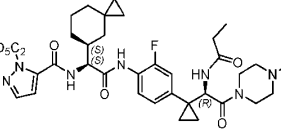
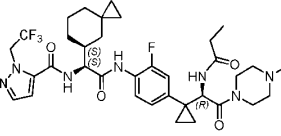
[0311] Examples in the table below were synthesized using conditions analogous to synthesis of Example **144**.

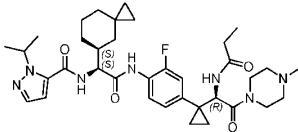
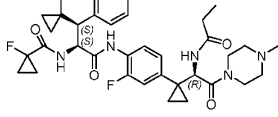
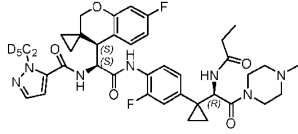
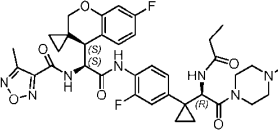
Ex. #	Structure Name	Spectral data
145	 <i>N</i> -((<i>S</i>)-1-(4,4-difluorocyclohexyl)-2-((2-fluoro-4-1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(4,4,4-trifluoro-3-hydroxybutyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 8.64 (d, <i>J</i> = 8.8 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.73 (dd, <i>J</i> = 8.4 Hz, 8.4 Hz, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 7.05 (m, 1H), 6.33 (d, <i>J</i> = 6.8 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.71-4.53 (m, 3H), 3.98-3.92 (m, 1H), 3.48-3.35 (m, 4H), 2.34-2.18 (m, 2H), 2.17-2.11 (m, 6H), 2.08-1.99 (m, 5H), 1.96-1.68 (m, 5H), 1.52-1.41 (m, 1H), 1.39-1.28 (m, 1H), 1.02-0.91 (m, 4H), 0.90-0.82 (m, 1H), 0.80-0.74 (m, 1H), 0.66-0.56 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 758.6.

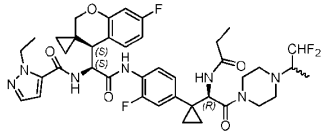
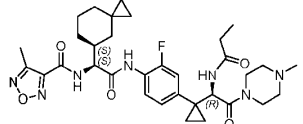
146	 1-((3,3-difluorocyclobutyl)methyl)-N-((S)-1-((S)-3,3-difluorocyclohexyl)-2-((4-(1-((R)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (m, 1H), 8.65 (d, <i>J</i> = 8.4 Hz, 1H), 8.09-7.97 (m, 1H), 7.73-7.62 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.14 (m, 2H), 7.07 (m, 1H), 6.05-5.62 (m, 1H), 5.27-5.13 (m, 1H), 4.74 (t, <i>J</i> = 8.0 Hz, 1H), 4.62-4.53 (d, <i>J</i> = 5.2 Hz, 2H), 4.42-4.32 (m, 1H), 3.92-3.83 (m, 1H), 3.01-2.88 (m, 1H), 2.61-2.38 (m, 6H), 2.21-1.91 (m, 6H), 1.81-1.60 (m, 6H), 1.47-1.32 (m, 1H), 1.30-1.02 (m, 3H), 0.98-0.73 (m, 6H), 0.68-0.57 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 771.4.
147	 1-(cyclopropylmethyl)-N-((S)-1-((S)-3,3-difluorocyclohexyl)-2-((4-(1-((R)-2-(4-(difluoromethyl)piperidin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-2-fluorophenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.95 (m, 1H), 8.60 (d, <i>J</i> = 8.4 Hz, 1H), 8.09-7.97 (m, 1H), 7.72-7.62 (m, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.23-7.14 (m, 2H), 7.02 (m, 1H), 6.04-5.62 (m, 1H), 5.22-5.15 (m, 1H), 4.73 (t, <i>J</i> = 8.0 Hz, 1H), 4.40-4.31 (m, 3H), 3.89 (m, 1H), 2.95 (m, 1H), 2.58-2.43 (m, 1H), 2.22-1.92 (m, 5H), 1.88-1.59 (m, 6H), 1.40 (m, 1H), 1.28-1.07 (m, 4H), 1.02-0.62 (m, 8H), 0.43-0.31 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 721.6.
148	 1-((3,3-difluorocyclobutyl)methyl)-N-((S)-1-((S)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((R)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (m, 1H), 8.66-8.62 (m, 1H), 8.12-7.97 (m, 1H), 7.83-7.63 (m, 1H), 7.50 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.14 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 5.26-5.13 (m, 1H), 4.76 (m, 1H), 4.61-4.59 (m, 2H), 4.45-4.35 (m, 1H), 3.90 (m, 1H), 2.98 (m, 1H), 2.63-2.32 (m, 6H), 2.23-1.93 (m, 5H), 1.85-1.60 (m, 6H), 1.43-1.15 (m, 4H), 1.12-0.50 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 789.4.
149	 N-((S)-2-((4-(1-((R)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-oxoethyl)-1H-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.64 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.66 (m, 1H), 7.54 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.15 (m, 2H), 7.07 (d, <i>J</i> = 2.0 Hz, 1H), 5.17 (m, 1H), 4.73 (m, 1H), 4.62-4.56 (m, 2H), 3.72-3.20 (m, 4H), 2.62-2.54 (m, 3H), 2.48-2.38 (m, 2H), 2.22-1.95 (m, 5H),

	fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-((3,3-difluorocyclobutyl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide	1.88-1.21 (m, 12H), 1.08-0.85 (m, 5H), 0.82-0.75 (m, 1H), 0.68-0.61 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 783.6.
150	 <i>N</i>-((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.98 (s, 1H), 8.73 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.68-7.62 (m, 2H), 7.24-7.15 (m, 3H), 6.46-6.18 (m, 1H), 5.19-5.16 (m, 1H), 5.02-4.92 (m, 2H), 4.77 (t, <i>J</i> = 8.0 Hz, 1H), 3.72-3.21 (m, 4H), 2.28-1.95 (m, 5H), 1.87-1.18 (m, 12H), 1.02-0.85 (m, 5H), 0.81-0.75 (m, 1H), 0.68-0.61 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 743.3.
151	 <i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(2,2-difluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96 (m, 1H), 8.74-8.71 (m, 1H), 8.12-7.98 (m, 1H), 7.83-7.62 (m, 2H), 7.24-7.10 (m, 3H), 6.46-6.18 (m, 1H), 5.27-5.13 (m, 1H), 5.01-4.90 (m, 2H), 4.81-4.71 (m, 1H), 4.40 (s, 1H), 3.92 (m, 1H), 3.02-2.93 (m, 1H), 2.60-2.57 (m, 1H), 2.23-1.95 (m, 5H), 1.82-1.62 (m, 6H), 1.42-1.33 (m, 2H), 1.31-1.12 (m, 2H), 1.09-0.58 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 749.8.
152	 <i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(2-fluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96-9.92 (m, 1H), 8.64-8.61 (m, 1H), 8.12-7.96 (m, 1H), 7.83-7.63 (m, 1H), 7.57 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.10 (m, 3H), 5.27-5.13 (m, 1H), 4.88-4.65 (m, 5H), 4.43-4.38 (m, 1H), 3.94-3.82 (m, 1H), 3.04-2.95 (m, 1H), 2.60-2.55 (m, 1H), 2.23-1.97 (m, 5H), 1.89-1.61 (m, 6H), 1.52-1.30 (m, 2H), 1.29-1.16 (m, 2H), 1.10-0.52 (m, 8H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 731.8.
153	 <i>N</i>-((<i>S</i>)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-((2-fluoro-4-(1-((<i>R</i>)-2-oxo-1-propionamido-2-(4-(trifluoromethyl)piperidin-1-yl)ethyl)cyclopropyl)phenyl)amino)-2-oxoethyl)-1-(2-fluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.96 (s, 1H), 8.61 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.70-7.64 (m, 1H), 7.50 (d, <i>J</i> = 2.0 Hz, 1H), 7.24-7.15 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.18-5.16 (m, 1H), 4.75 (t, <i>J</i> = 8.0

	<i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-(((<i>R</i>)-tetrahydrofuran-2-yl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H, 1H), 4.59-4.56 (m, 1H), 4.45-4.40 (m, 1H), 4.14-4.11 (m, 1H), 3.66-3.22 (m, 6H), 2.22-1.90 (m, 5H), 1.84-1.20 (m, 16H), 0.98-0.84 (m, 5H), 0.81-0.78 (m, 1H), 0.67-0.61 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 763.4.
154	 <i>N</i> -((<i>S</i>)-2-((4-(1-((<i>R</i>)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-3,3-difluorocyclohexyl)-2-oxoethyl)-1-((3-fluorobicyclo[1.1.1]pentan-1-yl)methyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.97 (s, 1H), 8.66 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.8 Hz, 1H), 7.69-7.63 (m, 1H), 7.53 (s, 1H), 7.22 (d, <i>J</i> = 8.4 Hz, 1H), 7.16 (d, <i>J</i> = 8.4 Hz, 1H), 7.05 (s, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.84 (s, 2H), 4.72 (t, <i>J</i> = 8.4 Hz, 1H), 3.71-3.21 (m, 4H), 2.22-1.97 (m, 5H), 1.84-1.22 (m, 18H), 0.98-0.86 (m, 5H), 0.82-0.78 (m, 1H), 0.68-0.64 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 777.3.
155	 1-(2,2-difluoroethyl)- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.93 (s, 1H), 8.61 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.60 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 3H), 6.45-6.16 (m, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 5.01-4.92 (m, 2H), 4.59 (t, <i>J</i> = 8.4 Hz, 1H), 3.46-3.28 (m, 4H), 2.23-1.94 (m, 9H), 1.72-1.67 (m, 2H), 1.60 (m, 1H), 1.48 (m, 1H), 1.35 (m, 1H), 1.20 (m, 2H), 1.00-0.94 (m, 5H), 0.87-0.74 (m, 3H), 0.63-0.58 (m, 1H), 0.28-0.15 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 686.4.
156	 1-(cyclopropylmethyl)- <i>N</i> -((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)-cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1 <i>H</i> -pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) 9.90 (s, 1H), 8.49 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.20-7.12 (m, 2H), 6.95 (d, <i>J</i> = 2.0 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.8 Hz, 1H), 4.33 (d, <i>J</i> = 7.2 Hz, 2H), 3.45-3.28 (m, 4H), 2.23-1.93 (m, 10H), 1.72-1.66 (m, 2H), 1.59 (m, 1H), 1.48 (m, 1H), 1.30 (m, 1H), 1.20 (m, 2H), 1.01-0.94 (m, 5H), 0.87-0.82 (m, 2H), 0.79-0.76 (m, 1H), 0.63-0.58 (m, 1H), 0.42-0.35 (m, 2H), 0.32-0.16 (m, 6H); LCMS (ESI, m/z): [M+H] ⁺ 676.5.

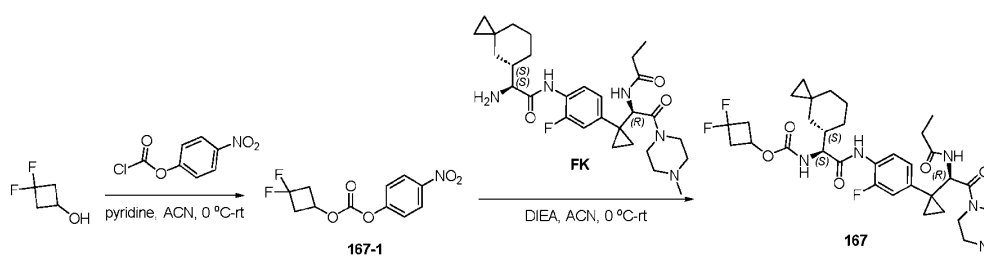
157	 1-fluoro-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)cyclopropane-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 8.02 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.0 Hz, 1H), 7.19-7.12 (m, 2H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.49 (t, <i>J</i> = 8.4 Hz, 1H), 3.45-3.27 (m, 4H), 2.25-1.92 (m, 10H), 1.72-1.53 (m, 3H), 1.43-1.12 (m, 7H), 1.02-0.91 (m, 5H), 0.88-0.72 (m, 3H), 0.61 (m, 1H), 0.30-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 614.4.
158	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-3-methylisoxazole-4-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.92 (s, 1H), 9.41 (s, 1H), 8.36 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.66 (t, <i>J</i> = 8.4 Hz, 1H), 7.19-7.12 (m, 2H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.61 (t, <i>J</i> = 8.4 Hz, 1H), 3.47-3.35 (m, 4H), 2.37 (s, 3H), 2.26-2.05 (m, 8H), 2.03-1.93 (m, 2H), 1.73-1.47 (m, 4H), 1.42-1.13 (m, 2H), 1.03-0.91 (m, 5H), 0.88-0.72 (m, 3H), 0.63-0.58 (m, 1H), 0.30-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 637.5.
159	 1-(ethyl-<i>d</i>₅)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.43 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.46 (d, <i>J</i> = 2.0 Hz, 1H), 7.18-7.11 (m, 2H), 6.96 (d, <i>J</i> = 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.56 (t, <i>J</i> = 8.4 Hz, 1H), 3.45-3.33 (m, 4H), 2.23-1.90 (m, 10H), 1.70-1.46 (m, 4H), 1.32-1.15 (m, 2H), 1.02-0.92 (m, 5H), 0.86-0.72 (m, 3H), 0.63-0.58 (m, 1H), 0.28-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 655.4.
160	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-(2,2,2-trifluoroethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.94 (s, 1H), 8.70 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.72-7.61 (m, 2H), 7.23-7.08 (m, 3H), 5.59-5.40 (m, 2H), 5.28 (d, <i>J</i> = 8.4 Hz, 1H), 4.60 (t, <i>J</i> = 8.8 Hz, 1H), 3.55-3.40 (m, 4H), 2.29-1.81 (m, 10H), 1.75-1.42 (m, 4H), 1.42-1.14 (m, 2H), 1.12-0.91 (m, 5H), 0.90-0.73 (m, 3H), 0.62-0.58 (m, 1H), 0.34-0.06 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 704.7.

161	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-1-isopropyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.89 (s, 1H), 8.42 (d, <i>J</i> = 8.4 Hz, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.70 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 1.6 Hz, 1H), 7.19-7.12 (m, 2H), 6.90 (d, <i>J</i> = 2.0 Hz, 1H), 5.40-5.35 (m, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 4.55 (t, <i>J</i> = 8.4 Hz, 1H), 3.46-3.28 (m, 4H), 2.25-1.96 (m, 10H), 1.72-1.45 (m, 4H), 1.39-1.31 (m, 7H), 1.27-1.15 (m, 1H), 1.02-0.92 (m, 5H), 0.86-0.73 (m, 3H), 0.62-0.57 (m, 1H), 0.28-0.14 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 664.5.
162	 1-fluoro-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)cyclopropane-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.23 (s, 1H), 8.53 (d, <i>J</i> = 9.6 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.72 (t, <i>J</i> = 8.4 Hz, 1H), 7.30-7.17 (m, 3H), 6.62-6.49 (m, 2H), 5.21 (d, <i>J</i> = 8.8 Hz, 1H), 4.98-4.93 (m, 2H), 3.49-3.35 (m, 5H), 2.59 (d, <i>J</i> = 10.0 Hz, 1H), 2.25-1.96 (m, 9H), 1.35-1.20 (m, 2H), 1.15-1.06 (m, 1H), 1.04-0.76 (m, 8H), 0.69-0.55 (m, 2H), 0.53-0.47 (m, 1H), 0.29-0.24 (m, 1H); LCMS (ESI, <i>m/z</i>): [M-H] ⁻ 680.2.
163	 1-(ethyl-<i>d</i>₅)-<i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.91 (d, <i>J</i> = 9.6 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.68 (t, <i>J</i> = 8.4 Hz, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.33-7.13 (m, 3H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.64-6.58 (m, 1H), 6.52-6.46 (m, 1H), 5.21 (d, <i>J</i> = 8.8 Hz, 1H), 5.13-5.05 (m, 2H), 3.49-3.38 (m, 5H), 2.57-2.53 (m, 1H), 2.25-1.97 (m, 9H), 1.05-0.92 (m, 4H), 0.88-0.77 (m, 3H), 0.68-0.58 (m, 2H), 0.54-0.48 (m, 1H), 0.32-0.25 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 723.3.
164	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-phenyl)amino)-1-((<i>S</i>)-7-	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.38 (s, 1H), 9.55 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.74 (t, <i>J</i> = 8.4 Hz, 1H), 7.24-7.17 (m, 3H), 6.67-6.60 (m, 1H), 6.58-6.53 (m, 1H), 5.23-5.11 (m, 2H), 5.04 (d, <i>J</i> = 12.4 Hz, 1H), 3.44-3.28 (m, 5H), 2.54-2.51 (m, 1H), 2.29 (s, 3H), 2.27-2.07 (m, 8H), 2.04-1.97 (m, 1H), 1.05-0.92 (m, 4H), 0.89-0.76 (m,

	fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-4-methyl-1,2,5-oxadiazole-3-carboxamide	3H), 0.67-0.59 (m, 2H), 0.56-0.48 (m, 1H), 0.35-0.28 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 706.4.
165	 <i>N</i>-((1<i>S</i>)-2-((4-(1-((1<i>R</i>)-2-(4-(1,1-difluoropropan-2-yl)piperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)-2-fluorophenyl)amino)-1-((<i>S</i>)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)-2-oxoethyl)-1-ethyl-1<i>H</i>-pyrazole-5-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.32 (s, 1H), 8.91 (d, <i>J</i> = 9.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.74-7.69 (m, 1H), 7.48 (d, <i>J</i> = 2.0 Hz, 1H), 7.31-7.17 (m, 3H), 6.99 (d, <i>J</i> = 2.0 Hz, 1H), 6.61 (m, 1H), 6.53-6.48 (m, 1H), 6.14-5.85 (m, 1H), 5.21 (d, <i>J</i> = 8.8 Hz, 1H), 5.14-5.06 (m, 2H), 4.36-4.28 (m, 2H), 3.37-3.27 (m, 5H), 2.97-2.85 (m, 1H), 2.58-2.54 (m, 1H), 2.50-2.25 (m, 4H), 2.22-2.07 (m, 2H), 1.17 (t, <i>J</i> = 7.2 Hz, 3H), 1.02-0.92 (m, 7H), 0.87-0.78 (m, 3H), 0.64-0.58 (m, 2H), 0.55-0.48 (m, 1H), 0.32-0.26 (m, 1H); LCMS (ESI, m/z): [M+H] ⁺ 782.5.
166	 <i>N</i>-((<i>S</i>)-2-((2-fluoro-4-(1-((<i>R</i>)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((<i>S</i>)-spiro[2.5]octan-5-yl)ethyl)-4-methyl-1,2,5-oxadiazole-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.99 (s, 1H), 9.09 (d, <i>J</i> = 8.4 Hz, 1H), 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.69 (t, <i>J</i> = 8.4 Hz, 1H), 7.20-7.13 (m, 2H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.64 (t, <i>J</i> = 8.0 Hz, 1H), 3.43-3.32 (m, 4H), 2.46 (s, 3H), 2.25-1.93 (m, 10H), 1.75-1.13 (m, 6H), 1.02-0.92 (m, 5H), 0.88-0.72 (m, 3H), 0.65-0.58 (m, 1H), 0.30-0.12 (m, 4H); LCMS (ESI, m/z): [M+H] ⁺ 638.5.

Example 167

3,3-difluorocyclobutyl ((*S*)-2-((2-fluoro-4-(1-((*R*)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)carbamate (167)



Step 1: 3,3-Difluorocyclobutyl (4-nitrophenyl) carbonate (167-1)

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[0312] To a solution of 3,3-difluorocyclobutan-1-ol (500 mg, 4.6 mmol) and pyridine (1.5 g, 19 mmol) in ACN (3 mL) at 0 °C under N₂ was added 4-nitrophenyl carbonochloridate (1.9 g, 9.4 mmol). After stirring for 3 hrs at rt, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (7:1), to afford 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (1 g). ¹H NMR (400 MHz, CDCl₃) δ 8.36-8.28 (m, 2H), 7.46-7.37 (m, 2H), 5.12-5.01 (m, 1H), 3.24-3.07 (m, 2H), 2.98-2.79 (m, 2H).

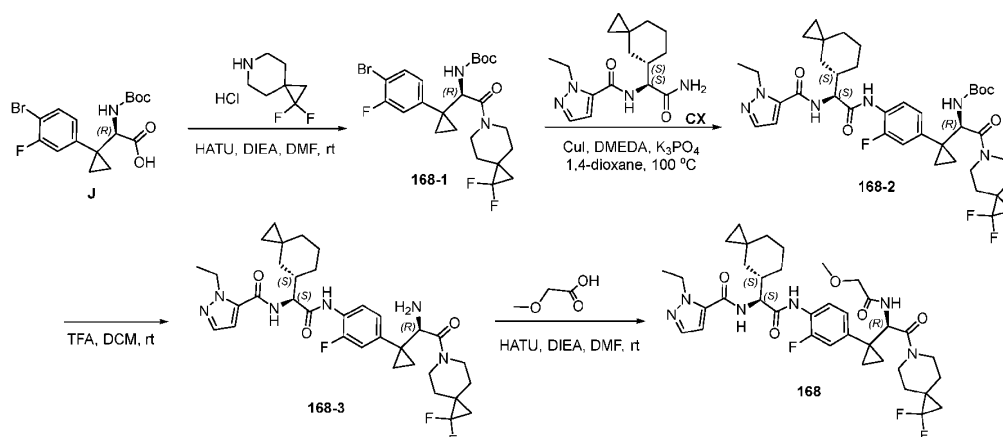
Step 2: 3,3-Difluorocyclobutyl ((S)-2-((2-fluoro-4-(1-((R)-2-(4-methylpiperazin-1-yl)-2-oxo-1-propionamidoethyl)cyclopropyl)phenyl)amino)-2-oxo-1-((S)-spiro[2.5]octan-5-yl)ethyl)carbamate (167)

[0313] To a solution of *N*-((*R*)-1-(1-(4-((*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (40 mg, 0.076 mmol) and DIEA (196 mg, 1.5 mmol) in ACN (2 mL) at 0 °C under N₂ was added 3,3-difluorocyclobutyl (4-nitrophenyl) carbonate (103 mg, 0.38 mmol). After stirring for 16 hrs at rt, the mixture was treated with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (9:1), to afford impure product. The material was further purified by prep-HPLC (0.05% NH₄HCO₃) to Example 167. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.75 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.22-7.11 (m, 2H), 5.19 (d, *J* = 8.8 Hz, 1H), 4.83-4.72 (m, 1H), 4.11 (t, *J* = 8.4 Hz, 1H), 3.49-3.26 (m, 4H), 3.06-2.94 (m, 2H), 2.70-2.54 (m, 2H), 2.27-2.04 (m, 8H), 2.02-1.92 (m, 1H), 1.90-1.73 (m, 1H), 1.70-1.52 (m, 3H), 1.47 (m, 1H), 1.30 (m, 1H), 1.15 (m, 1H), 1.02-0.73 (m, 8H), 0.62-0.57 (m, 1H), 0.30-0.11 (m, 4H); LCMS (ESI, *m/z*): [M+H]⁺ 662.4.

Example 168

N-((*S*)-2-((4-(1-((*R*)-2-(1,1-Difluoro-6-azaspiro[2.5]octan-6-yl)-1-(2-methoxyacetamido)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (168)

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Step 1: *tert*-Butyl (*R*)-(1-(1-(4-bromo-3-fluorophenyl)cyclopropyl)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)carbamate (**168-1**)

[0314] Intermediate **168-1** was synthesized following conditions analogous to synthesis of **B-1A**. LCMS (ESI, *m/z*): [*M*+*H*]⁺ 517.2.

Step 2: *tert*-Butyl ((*R*)-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-1-(1-(4-((*S*)-2-(1-ethyl-1*H*-pyrazole-5-carboxamido)-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-oxoethyl)carbamate (**168-2**)

[0315] Intermediate **168-2** was synthesized following conditions analogous to synthesis of **FK-3**. LCMS (ESI, *m/z*): [*M*+*H*]⁺ 741.5.

Step 3: *N*-((*S*)-2-((4-(1-((*R*)-1-Amino-2-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**168-3**)

[0316] Intermediate **168-3** was synthesized following conditions analogous to synthesis of **V-5**. LCMS (ESI, *m/z*): [*M*+*H*]⁺ 641.2.

Step 4: *N*-((*S*)-2-((4-(1-((*R*)-2-(1,1-Difluoro-6-azaspiro[2.5]octan-6-yl)-1-(2-methoxyacetamido)-2-oxoethyl)cyclopropyl)-2-fluorophenyl)amino)-2-oxo-1-((*S*)-spiro[2.5]octan-5-yl)ethyl)-1-ethyl-1*H*-pyrazole-5-carboxamide (**168**)

[0317] Example **168** was synthesized following conditions analogous to synthesis of

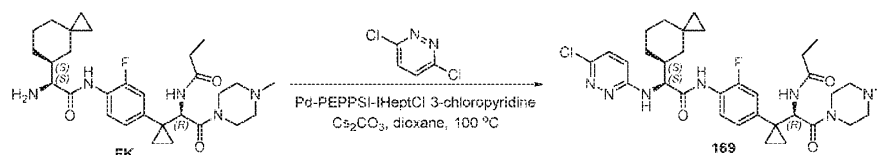
Example **144**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.71-7.64 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.19-7.10 (m, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 5.10 (t, *J* = 7.6 Hz, 1H), 4.55 (t, *J* = 8.4 Hz, 1H), 4.46 (q, *J* = 6.8 Hz, 2H), 3.86 (m, 2H), 3.65-3.34 (m,

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4H), 3.32 (s, 3H), 2.08-2.00 (m, 1H), 1.72-1.46 (m, 7H), 1.38-1.17 (m, 8H), 1.05-0.94 (m, 3H), 0.85-0.77 (m, 3H), 0.28-0.15 (m, 4H); LCMS (ESI, m/z): [M+H]⁺ 713.5.

Example 169

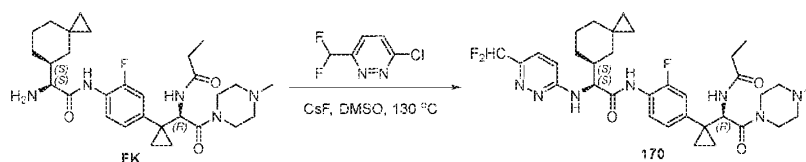
N-((*R*)-1-(1-(4-((*S*)-2-((6-chloropyridazin-3-yl)amino)-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**169**)



[0318] A mixture of *N*-((*R*)-1-(1-(4-((*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (40 mg, 0.076 mmol), 3,6-dichloropyridazine (22 mg, 0.15 mmol), Cs₂CO₃ (74 mg, 0.23 mmol), Pd-PEPPSI-IHeptCl 3-chloropyridine (7 mg, 0.008 mmol) in 1,4-dioxane (1 mL) was degassed and backfilled with N₂. After stirring at 100 °C for 16 hr, the mixture was concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (10:1), to give impure product. The material was further purified by prep-HPLC (0.05% NH₄HCO₃) to afford Example **169**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.89 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.64 (t, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.17-7.09 (m, 2H), 7.07 (d, *J* = 9.2 Hz, 1H), 5.18 (d, *J* = 8.8 Hz, 1H), 4.71 (t, *J* = 7.6 Hz, 1H), 3.49-3.32 (m, 4H), 2.23-2.05 (m, 8H), 2.01-1.91 (m, 2H), 1.75-1.67 (m, 2H), 1.61 (t, *J* = 12.4 Hz, 2H), 1.42-1.21 (m, 2H), 1.02-0.93 (m, 5H), 0.87-0.73 (m, 3H), 0.62-0.57 (m, 1H), 0.31-0.15 (m, 4H); LCMS (ESI, m/z): [M+H]⁺ 640.4.

Example 170

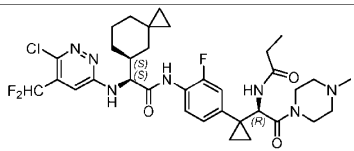
N-((*R*)-1-(1-(4-((*S*)-2-((6-(difluoromethyl)pyridazin-3-yl)amino)-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (**170**)

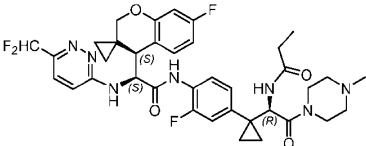
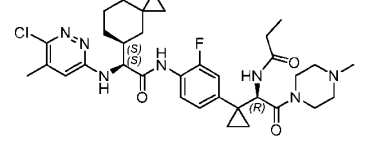
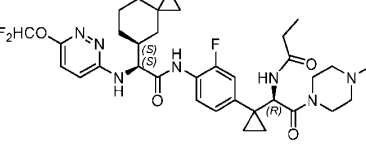


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[0319] A solution of *N*-((*R*)-1-(1-(4-((*S*)-2-amino-2-((*S*)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide (100 mg, 0.190 mmol), 3-chloro-6-(difluoromethyl)pyridazine (31 mg, 0.19 mmol) and CsF (43 mg, 0.29 mmol) in DMSO (1 mL) was stirred at 130 °C for 5 hrs under N₂. The mixture was treated with water and extracted with EtOAc. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM/MeOH (20:1), to afford impure product. The material was further purified by prep-HPLC (0.05% NH₄HCO₃) followed by prep-chiral-HPLC (Column: CHIRALPAK IG, 2*25 cm, 5 μm; mobile phase A: Hex (0.5% 2 M NH₃-MeOH), mobile phase B: EtOH:DCM=1: 1; flow rate: 20 mL/min; gradient (B%): isocratic 60%; wave length: 254/220 nm) to afford Example **170**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.94 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.55-7.48 (m, 2H), 7.18-6.81 (m, 4H), 5.18 (d, *J* = 8.8 Hz, 1H), 4.84 (t, *J* = 7.6 Hz, 1H), 3.45-3.26 (m, 4H), 2.22-1.95 (m, 10H), 1.75-1.58 (m, 4H), 1.41-1.22 (m, 2H), 1.02-0.93 (m, 5H), 0.85-0.72 (m, 3H), 0.59 (m, 1H), 0.29-0.17 (m, 4H); LCMS (ESI, *m/z*): [M+H]⁺ 656.4.

[0320] Examples **171** was synthesized using conditions analogous to synthesis of **170**.
 Examples **172** and **173** were synthesized using conditions analogous to synthesis of **169**.
 Example **174** was synthesized using Gphos G6 Pd TES and Gphos as catalysts for C-N coupling reaction.

Ex. #	Structure Name	Spectral data
171	 <i>N</i>-((<i>R</i>)-1-(1-(4-((<i>S</i>)-2-((<i>S</i>)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.95 (s, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.65-7.57 (m, 2H), 7.35 (s, 1H), 7.20-6.94 (m, 3H), 5.19 (d, <i>J</i> = 8.8 Hz, 1H), 4.77 (t, <i>J</i> = 7.6 Hz, 1H), 3.43-3.33 (m, 4H), 2.22-1.92 (m, 10H), 1.72-1.56 (m, 4H), 1.42-1.28 (m, 2H), 1.02-0.91 (m, 5H), 0.86-0.71 (m, 3H), 0.62-0.57 (m, 1H), 0.29-0.15 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 690.4.

172	 <i>N-((R)-1-(1-(4-((S)-2-((6-(difluoromethyl)pyridazin-3-yl)amino)-2-((S)-7-fluorospiro[chromane-3,1'-cyclopropan]-4-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide</i>	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.35 (s, 1H), 8.03 (d, <i>J</i> = 8.8 Hz, 1H), 7.85 (d, <i>J</i> = 9.6 Hz, 1H), 7.70 (t, <i>J</i> = 8.4 Hz, 1H), 7.50 (d, <i>J</i> = 9.6 Hz, 1H), 7.24-7.14 (m, 3H), 7.08 (d, <i>J</i> = 9.2 Hz, 1H), 6.90 (t, <i>J</i> = 54.8 Hz, 1H), 6.57 (m, 1H), 6.47 (m, 1H), 5.44 (t, <i>J</i> = 8.8 Hz, 1H), 5.20 (d, <i>J</i> = 8.8 Hz, 1H), 5.07 (d, <i>J</i> = 11.2 Hz, 1H), 3.42-3.25 (m, 5H), 2.51-2.45 (m, 1H), 2.23-2.06 (m, 8H), 2.02-2.00 (m, 1H), 1.01-0.93 (m, 4H), 0.91-0.76 (m, 3H), 0.65-0.58 (m, 2H), 0.54-0.47 (m, 1H), 0.45-0.38 (m, 1H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 724.4.
173	 <i>N-((R)-1-(1-(4-((S)-2-((6-chloro-5-methylpyridazin-3-yl)amino)-2-((S)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide</i>	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.88 (s, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.66 (t, <i>J</i> = 8.4 Hz, 1H), 7.17-7.09 (m, 3H), 6.96 (s, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.69 (t, <i>J</i> = 8.0 Hz, 1H), 3.47-3.26 (m, 4H), 2.25-2.06 (m, 11H), 2.01-1.90 (m, 2H), 1.73-1.68 (m, 2H), 1.63-1.56 (m, 2H), 1.41-1.22 (m, 2H), 1.01-0.92 (m, 5H), 0.84-0.72 (m, 3H), 0.62-0.57 (m, 1H), 0.28-0.19 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 654.4.
174	 <i>N-((R)-1-(1-(4-((S)-2-((6-(difluoromethoxy)pyridazin-3-yl)amino)-2-((S)-spiro[2.5]octan-5-yl)acetamido)-3-fluorophenyl)cyclopropyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl)propionamide</i>	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.82 (s, 1H), 8.00 (d, <i>J</i> = 8.8 Hz, 1H), 7.79-7.43 (m, 2H), 7.20-7.08 (m, 4H), 7.04 (d, <i>J</i> = 8.0 Hz, 1H), 5.18 (d, <i>J</i> = 8.8 Hz, 1H), 4.64 (t, <i>J</i> = 7.6 Hz, 1H), 3.50-3.26 (m, 4H), 2.28-2.05 (m, 8H), 2.02-1.91 (m, 2H), 1.78-1.67 (m, 2H), 1.67-1.55 (m, 2H), 1.43-1.26 (m, 2H), 1.04-0.91 (m, 5H), 0.88-0.70 (m, 3H), 0.64-0.55 (m, 1H), 0.32-0.13 (m, 4H); LCMS (ESI, <i>m/z</i>): [M+H] ⁺ 672.5.

Biological Example 1. IL17-AA HEK Cell Reporter Assay

[0321] Human embryonic kidney HEK293 cells with a stably intergraded human IL-17 receptor (RA/RC) signal-dependent secreted embryonic alkaline phosphatase (SEAP) reporter gene (Invivogen, Cat# hkb-il17) were plated in DMEM (Hyclone) containing 10% heat-inactivated FBS (Thermo Fisher) and 100 U/mL PenStrep (Solarbio). The cells were

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treated with serial diluted compounds and stimulated with human recombinant IL17-AA protein (R&D, Cat# 7955-IL-025) overnight. Activity of SEAP was then detected from the cell cultured supernatant according to the manufacturer's instructions. Inhibition data were calculated by comparison to vehicle control (Hc) wells for 0% inhibition and non-stimulated control (Lc) wells for 100% inhibition following the equation below:

$$\% \text{ Inhibition} = (\text{RHc} - \text{RSample}) / (\text{RHc} - \text{RLc}) * 100$$

Dose response curves were then generated to determine the concentration required to suppress 50% of cellular response (IC₅₀) using XLFit (equation 201).

[0322] For IL-17AA HEK Blue activity, bracket is denoted as: A < 50 nM; 50 nM < B < 500 nM; > 500 nM < C < 20000 nM.

Example	17AA IC ₅₀	Example	17AA IC ₅₀	Example	17AA IC ₅₀
1	A	59	A	117	A
2	A	60	A	118	A
3	B	61	A	119	A
4	A	62	A	120	A
5	A	63	A	121	A
6	A	64	A	122	A
7	A	65	A	123	A
8	A	66	A	124	A
9	A	67	A	125	A
10	A	68	A	126	A
11	A	69	A	127	A
12	A	70	A	128	A
13	A	71	A	129	A
14	A	72	A	130	A
15	A	73	A	131	A
16	A	74	A	132	A
17	A	75	A	133	A
18	A	76	A	134	A
19	A	77	A	135	A
20	A	78	A	136	A
21	A	79	A	137	A
22	A	80	A	138	A
23	A	81	A	139	A
24	A	82	A	140	A
25	A	83	A	141	A
26	A	84	A	142	A
27	A	85	A	143	A
28	A	86	A	144	A
29	A	87	A	145	A
30	A	88	A	146	A
31	A	89	A	147	A

32	A	90	A	148	A
33	A	91	A	149	A
34	A	92	A	150	A
35	A	93	A	151	A
36	A	94	A	152	A
37	A	95	A	153	A
38	A	96	A	154	A
39	A	97	A	155	A
40	A	98	A	156	A
41	A	99	A	157	A
42	A	100	A	158	A
43	A	101	A	159	A
44	A	102	A	160	A
45	A	103	A	161	A
46	A	104	A	162	A
47	A	105	A	163	A
48	A	106	A	164	A
49	A	107	A	165	A
50	A	108	A	166	A
51	A	109	A	167	A
52	A	110	A	168	A
53	A	111	A	169	A
54	A	112	A	170	A
55	A	113	A	171	A
56	A	114	A	172	A
57	A	115	A	173	A
58	A	116	A	174	A

Biological Example 2. IL17-AF HEK Cell Reporter Assay

[0323] Human embryonic kidney HEK293 cells with a stably integrated human IL-17 receptor (RA/RC) signal dependent secreted embryonic alkaline phosphatase (SEAP) reporter gene (Invivogen, Cat# hkb-il17) were plated in DMEM (Hyclone) containing 10% heat-inactivated FBS (Thermo Fisher) and 100 U/mL PenStrep (Solarbio). The cells were treated with serial diluted compounds and stimulated with human recombinant IL17-AF protein (R&D, Cat# 5837-IL-010) overnight. Activity of SEAP was then detected from the cell cultured supernatant according to the manufacturer's instructions. Inhibition data were calculated by comparison to vehicle control (Hc) wells for 0% inhibition and non-stimulated control (Lc) wells for 100% inhibition following the equation below:

$$\% \text{ Inhibition} = (\text{RHc} - \text{RSample}) / (\text{RHc} - \text{RLc}) * 100$$

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Dose response curves were then generated to determine the concentration required to suppress 50% of cellular response (IC₅₀) using XLFit (equation 201).

Examples 2, 7, 9, 11, 26, 31, 33, 45, 49, 54, 59, 88, 93, 95, 96, 102, 111, 120, 123, 125, 128, 132, 135, 139, 140, 141, 143, 144, 147 and 158 exhibited IC₅₀ values less than 100 nM in the IL-17AF HEK Blue.

[0324] The Summary and Abstract sections may set forth one or more but not all exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[0325] The present invention has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0326] With respect to aspects of the invention described as a genus, all individual species are individually considered separate aspects of the invention. If aspects of the invention are described as "comprising" a feature, embodiments also are contemplated "consisting of" or "consisting essentially of" the feature.

[0327] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0328] The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments.

[0329] All of the various aspects, embodiments, and options described herein can be combined in any and all variations.

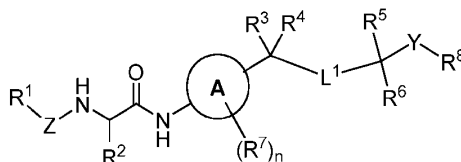
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[0330] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern.

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WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

- R¹** is an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;
- Z** is null, C(O), -C(O)-O-, or -C(O)-N(G^Z)-, wherein when Z is -C(O)-O-, or -C(O)-N(G^Z)-, the carbonyl group is bonded with the adjacent NH group in Formula I, and wherein G^Z is hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring;
- R²** is an optionally substituted carbocyclyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, or an optionally substituted alkyl;
- Ring A** is phenylene or 5- or 6-membered heteroarylene (e.g., pyridylene, pyridazinylen, pyrimidinylene, etc.), which is optionally substituted with 1-4 instances of R⁷ as valency permits;
- R³ and R⁴** are each independently F, CN, G^{1A}, or J¹-J²-J³-G^{1B}, wherein J¹, J², and J³ are each independently null, O, NG^{1B}, C(O), S, SO, SO₂, or P(O)G^{1B}, provided that at least one of J¹, J², and J³ is not null, and wherein:
- G^{1B} at each occurrence is independently hydrogen or G^{1A}, and
- G^{1A} at each occurrence is independently an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring (preferably optionally substituted C₃₋₈ carbocyclic ring, or optionally substituted 4-8 membered heterocyclic ring);

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or **R³ and R⁴**, together with the carbon atom they are both attached to, are joined to form an optionally substituted 3-8 membered carbocyclic or 4-8 membered heterocyclic ring;

L¹ is null, an optionally substituted C₁₋₄ alkylene, or an optionally substituted C₁₋₄ heteroalkylene,

R⁵ is hydrogen, deuterium, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, or optionally substituted 3-8 membered ring;

or either **R³ or R⁴**, together with **R⁵**, and the intervening atoms, are joined to form an optionally substituted 3-8 membered carbocyclic or 4-8 membered heterocyclic ring;

R⁶ is O-G^{2A}, N(G^{2A})C(O)G^{2A}, N(G^{2A})C(O)OG^{2B}, N(G^{2A})C(O)NG^{2A}G^{2A}, N(G^{2A})SO₂G^{2B}, or N(G^{2A})SO₂NG^{2A}G^{2A}, wherein G^{2A} at each occurrence is independently hydrogen or G^{2B}; and wherein G^{2B} at each occurrence is independently an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C₃₋₈ carbocyclic ring, optionally substituted 5- or 6-membered heteroaryl ring, or optionally substituted 4-8 membered heterocyclic ring),

Y is C(O) or SO₂;

R⁸ is NG³G³, an optionally substituted 4-14 membered heterocyclic ring, or an optionally substituted heteroaryl ring, wherein:

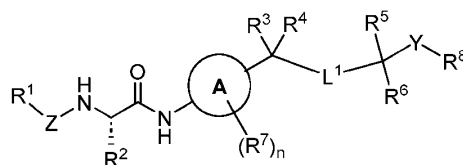
G³ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₃₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring; or two G³, together with the nitrogen atom they are both attached to, are joined to form an optionally substituted 4-8 membered heterocyclic ring;

R⁷ at each occurrence is independently deuterium, halogen, CN, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, optionally substituted 3-8 membered ring, or J⁴-J⁵-J⁶-G⁴, wherein J⁴, J⁵, and J⁶ are each independently null, O, NG⁴, C(O), S, SO, SO₂, or P(O)G⁴, wherein at least one of J⁴, J⁵, and J⁶ is not null, and wherein G⁴ at each occurrence is independently hydrogen, an optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ heteroalkyl, or optionally substituted 3-8 membered ring; or two R⁷ can be joined to form an optionally substituted 4-8 membered ring;

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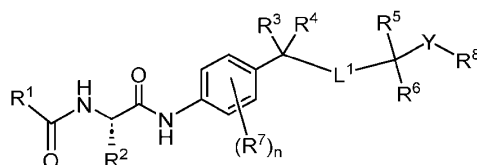
or one instance of R^7 and either R^3 or R^4 , together with the intervening atoms, are joined to form an optionally substituted 5-8 membered carbocyclic or heterocyclic ring; and "n" is an integer selected from 0-4.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-E1:



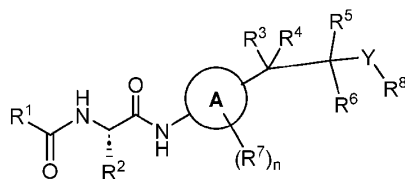
Formula I-E1.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Ring A is phenylene and the compound is characterized as having a structure according to Formula I-1:



Formula I-1.

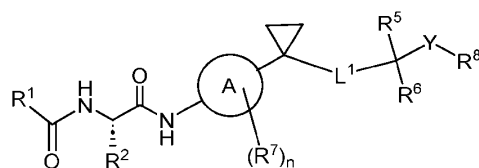
4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-2:



Formula I-2.

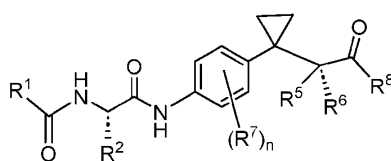
5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-3:

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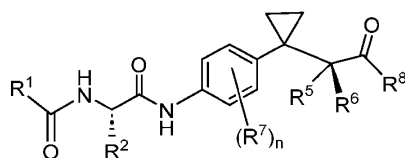


Formula I-3.

6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-4 or I-4-D2:



Formula I-4



Formula I-4-D2.

7. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein Z is C(O).
8. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R¹ is an optionally substituted 5- or 6-membered heteroaryl, preferably, a substituted 5- or 6-membered heteroaryl.
9. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R¹ is a 5- or 6-membered heteroaryl selected from pyrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, furan, thiophene, imidazole, oxadiazole, thiadiazole, triazole, tetrazole, pyridine, pyrimidine, pyrazine, and pyridazine, each of which is optionally substituted with one or more substituents independently selected from

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halogen, CN, OH, NH₂, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, NR^{A1}R^{A1}, NR^{A1}SO₂R^{A1}, C(O)R^{A1}, C(O)NHR^{A1}, C(O)NR^{A1}R^{A1}, S(O)_qR^{A1}, S(O)_qNR^{A1}R^{A1}, and S(O)(=NR^{A1})R^{A1},

wherein

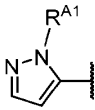
q is 1 or 2; and

R^{A1} at each occurrence is independently C₁₋₆ alkyl, C₃₋₁₀ carbocyclic, or 4-10 membered heterocyclic ring, wherein:

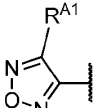
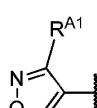
the C₁₋₆ alkyl is optionally substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring (e.g., cyclopropyl, cyclobutyl, etc.), wherein the C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH; and

the C₃₋₁₀ carbocyclic or 4-10 membered heterocyclic ring is optionally substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ alkyl, C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH.

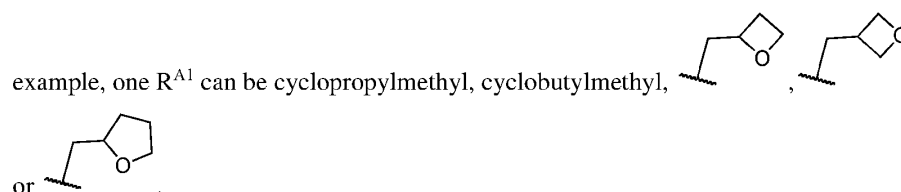
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R¹ has

a structure according to , wherein R^{A1} is as defined in claim 9.

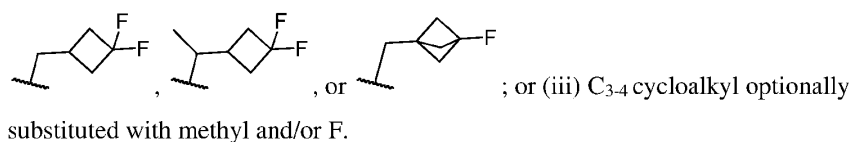
11. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein R¹ has

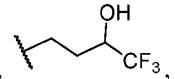
a structure according to  or , wherein R^{A1} is as defined in claim 9.

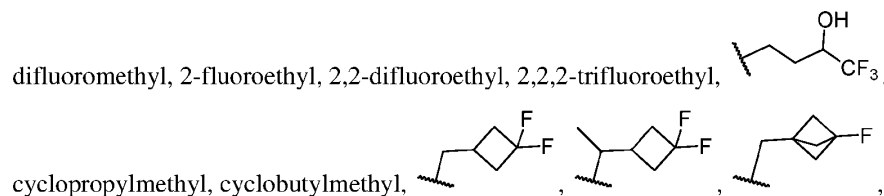
12. The compound of any of claims 9-11, or a pharmaceutically acceptable salt thereof, wherein R^{A1} at each occurrence is independently (1) C_{1-4} alkyl optionally substituted with one or more substituents independently selected from deuterium, F, and OH, or (2) a C_{3-6} cycloalkyl optionally substituted with one or more substituents independently selected from deuterium, methyl, F, and OH; (3) a 4-6 membered heterocyclyl optionally substituted with one or more substituents independently selected from deuterium, methyl, CD_3 , F, and OH; or (4) (C_{1-3} alkylene)-(3-6 membered ring), wherein the C_{1-3} alkylene and 3-6 membered ring are each independently optionally substituted with one or more substituents independently selected from deuterium, methyl, CD_3 , F, and OH, wherein the 3-6 membered ring is a C_{3-6} cycloalkyl or 4-6 membered heterocyclyl, for

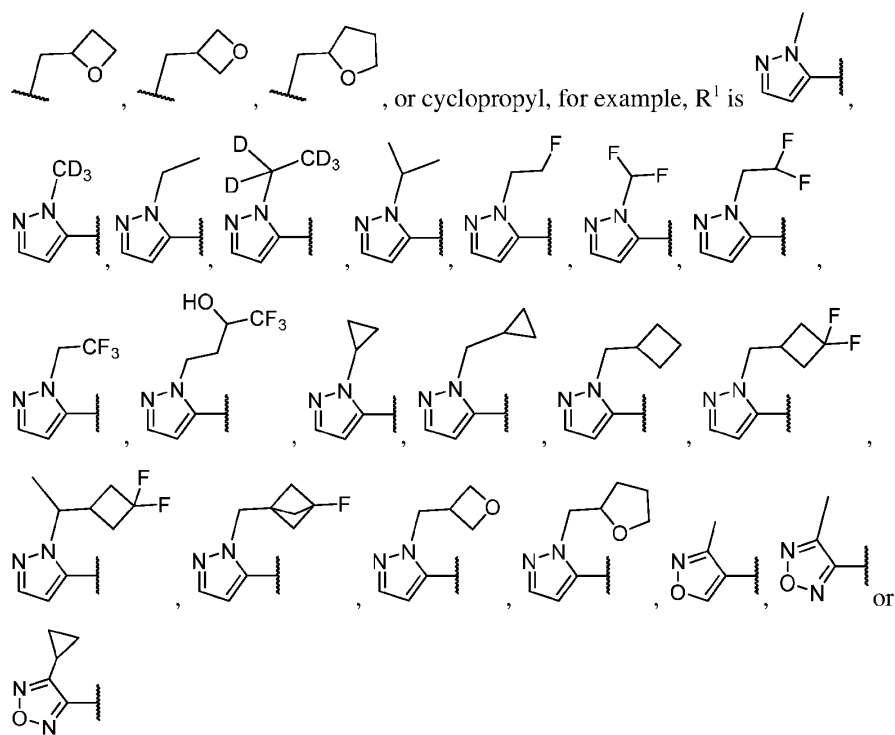


13. The compound of any of claims 9-11, or a pharmaceutically acceptable salt thereof, wherein R^{A1} at each occurrence is independently (i) C_{1-4} alkyl optionally substituted with deuterium and/or F, (ii) (C_{1-2} alkylene)- C_{3-5} cycloalkyl, such as cyclopropylmethyl, cyclobutylmethyl, wherein the C_{1-2} alkylene and C_{3-5} cycloalkyl are each independently optionally substituted with methyl, deuterium, and/or F; for example, one R^{A1} is



14. The compound of any of claims 9-11, or a pharmaceutically acceptable salt thereof, wherein R^{A1} at each occurrence is independently methyl, CD_3 , ethyl, CD_2CD_3 , isopropyl, difluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, ,





15. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^2 is an optionally substituted 3-14 membered carbocyclyl, which is monocyclic or polycyclic, and wherein when substituted, the 3-14 membered carbocyclyl is preferably substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2} , SR^{A2} , $NR^{A2}R^{A2}$, $C(O)R^{A2}$, $C(O)OR^{A2}$, $C(O)NR^{A2}R^{A2}$, $S(O)R^{A2}$, SO_2R^{A2} , $SO_2NR^{A2}R^{A2}$, $OC(O)R^{A2}$, $NR^{A2}C(O)R^{A2}$, $NR^{A2}SO_2R^{A2}$, $PO(R^{A2})(R^{A2})$, or R^{B2} , wherein R^{A2} at each occurrence is independently hydrogen or R^{B2} , and wherein R^{B2} at each occurrence is independently an optionally substituted group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or a 3-7 membered carbocyclic or 4-7 membered heterocyclic ring, wherein, when substituted,

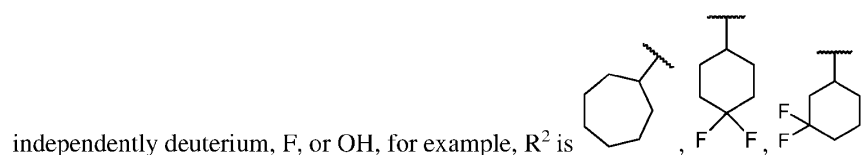
the C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents

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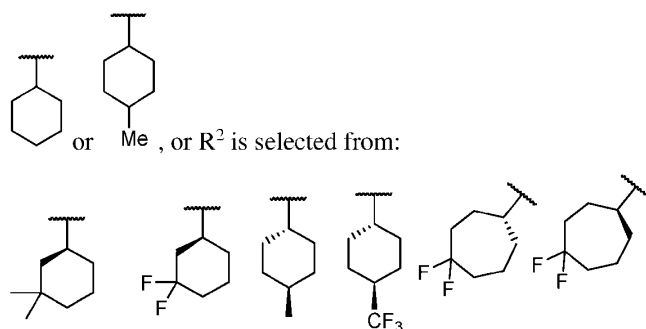
independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH; and

the 3-7 membered carbocyclic or 4-7 membered heterocyclic ring is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ alkyl, C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R² is a monocyclic C₃₋₈ cycloalkyl, optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F.
17. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R² is a monocyclic C₃₋₇ cycloalkyl, such as cyclohexyl or cycloheptyl, which is optionally substituted with one or more substituents each independently deuterium, F, or C₁₋₃ alkyl optionally substituted with one or more G^{S2}, wherein G^{S2} at each occurrence is

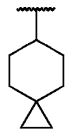
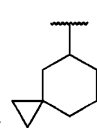


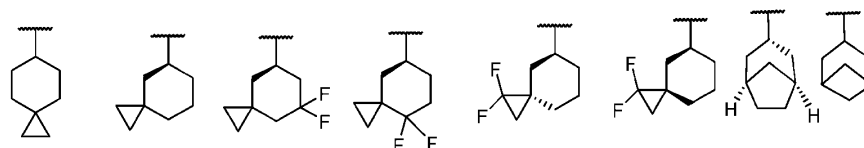
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18. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R² is a polycyclic C₄₋₁₀ carbocyclyl, e.g., spiro [2,5] octanyl, indanyl, etc., optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F.

19. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R² is

a spiro, fused, or bridged bicyclic C₄₋₁₀ cycloalkyl, e.g.,  or , which is optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ alkoxy optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, for example, R² is selected from:



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20. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof,



wherein R² has a structure of , wherein

- R¹⁰ and R¹¹ are each independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted C₃₋₇ carbocyclic, or optionally substituted phenyl, wherein at least one of R¹⁰ and R¹¹ is not hydrogen, preferably, both of R¹⁰ and R¹¹ are not hydrogen.
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is a C₁₋₄ alkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, e.g., R¹⁰ is an unsubstituted C₁₋₄ alkyl.
22. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (1) a C₃₋₆ cycloalkyl; or (2) -(C₁₋₃ alkylene)-(C₃₋₆ cycloalkyl), wherein each of the C₁₋₃ alkylene and C₃₋₆ cycloalkyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, for example, R¹⁰ is cyclopropyl, methylcyclopropyl, or cyclobutyl.
23. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (1) a phenyl; or (2) -(C₁₋₃ alkylene)-phenyl, wherein each of the C₁₋₃ alkylene and phenyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, CN, C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or C₁₋₄ heteroalkyl optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, for example, R¹⁰ is phenyl or halogen substituted phenyl, such as 2-chlorophenyl.

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24. The compound of any of claims 20-23, or a pharmaceutically acceptable salt thereof, wherein R^{11} is (1) a C_{3-6} cycloalkyl; or (2) $-(C_{1-3} \text{ alkylene})-(C_{3-6} \text{ cycloalkyl})$, wherein each of the C_{1-3} alkylene and C_{3-6} cycloalkyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, for example, R^{11} is cyclopropyl, methylcyclopropyl, or cyclobutyl.
25. The compound of any of claims 20-23, or a pharmaceutically acceptable salt thereof, wherein R^{11} is (1) a phenyl; or (2) $-(C_{1-3} \text{ alkylene})\text{-phenyl}$, wherein each of the C_{1-3} alkylene and phenyl is optionally substituted, for example, with one or more substituents each independently deuterium, halogen, OH, oxo, CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, for example, R^{11} is phenyl or halogen substituted phenyl, such as 2-chlorophenyl.
26. The compound of any of claims 20-25, or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^{11} are the same.
27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^{11} are both cyclopropyl, cyclobutyl, or phenyl.
28. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein R^2 is an optionally substituted 10-14 membered polycyclic heterocyclyl having 1-3 ring heteroatoms independently selected from S, O, and N, and wherein when substituted, the 10-14 membered polycyclic heterocyclyl is preferably substituted with one or more substituents each independently deuterium, halogen, CN, oxo, OR^{A2} , SR^{A2} , $NR^{A2}R^{A2}$, $C(O)R^{A2}$, $C(O)OR^{A2}$, $C(O)NR^{A2}R^{A2}$, $S(O)R^{A2}$, SO_2R^{A2} , $SO_2NR^{A2}R^{A2}$, $OC(O)R^{A2}$, $NR^{A2}C(O)R^{A2}$, $NR^{A2}SO_2R^{A2}$, $PO(R^{A2})(R^{A2})$, or R^{B2} ,
 wherein R^{A2} at each occurrence is independently hydrogen or R^{B2} , and

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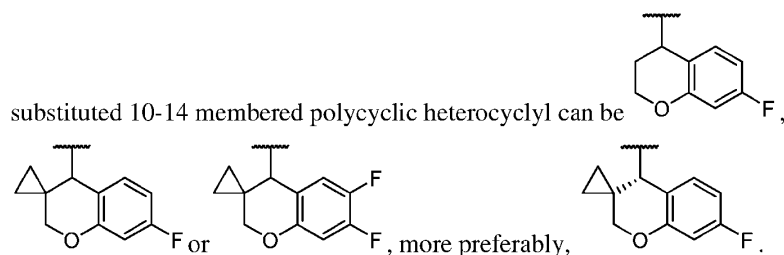
wherein R^{B2} at each occurrence is independently an optionally substituted group selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or a 3-7 membered carbocyclic or 4-7 membered heterocyclic ring, wherein, when substituted,

the C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH; and

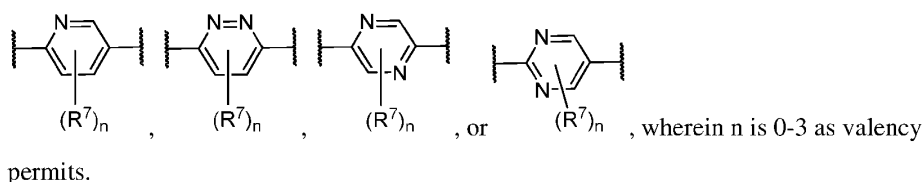
the 3-7 membered carbocyclic or 4-7 membered heterocyclic ring is preferably substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, oxo, and 3-8 membered ring, wherein the C₁₋₆ alkyl, C₁₋₆ heteroalkyl and 3-8 membered ring are optionally substituted with one or more substituents independently selected from deuterium, halogen, oxo, OH, C₁₋₃ alkyl optionally substituted with deuterium, halogen and/or OH, or 3-5 membered ring optionally substituted with C₁₋₃ alkyl, halogen, and/or OH.

29. The compound of claim 28, or a pharmaceutically acceptable salt thereof, wherein the optionally substituted 10-14 membered polycyclic heterocyclyl is optionally substituted with one or more substituents each independently halogen, CN, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, wherein the 10-14 membered polycyclic heterocyclyl has a fused ring structure from a 5-7 membered heterocyclic ring and a phenyl or 6-membered heteroaryl ring, optionally one additional ring which forms a spiro, fused, or bridged structure with the 5-7 membered heterocyclic ring; preferably, the 10-14 membered polycyclic heterocyclyl has a fused ring structure from a 6 membered heterocyclic ring having one ring heteroatom which is O, N, or S, and a phenyl ring, optionally also contains a spiro cyclopropyl ring to the 6 membered heterocyclic ring, for example, the optionally

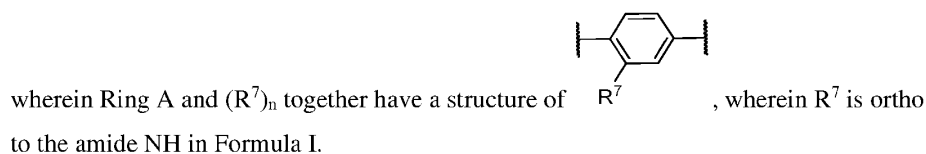
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30. The compound of any of claims 1, 2, 4, 5, and 7-29, or a pharmaceutically acceptable salt thereof, wherein as applicable, Ring A and $(R^7)_n$ together have a structure of

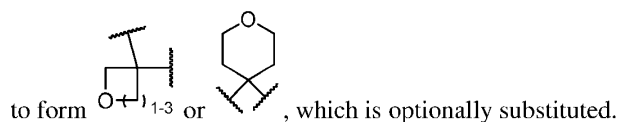


31. The compound of any of claims 1-29, or a pharmaceutically acceptable salt thereof,

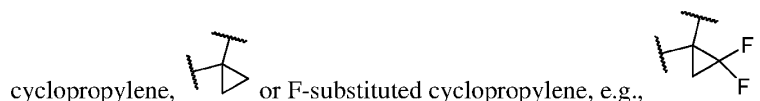


32. The compound of any of claims 1-4 and 7-31, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each independently C_{1-4} alkyl optionally substituted with one or more G^{S2} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S2} , wherein G^{S2} at each occurrence is independently deuterium, F, or OH.
33. The compound of any of claims 1-4 and 7-32, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-4} alkyl optionally substituted with deuterium and/or F, e.g., R^3 is methyl.
34. The compound of any of claims 1-4 and 7-33, or a pharmaceutically acceptable salt thereof, wherein R^4 is C_{1-4} alkyl optionally substituted with deuterium and/or F, e.g., R^4 is methyl.

35. The compound of any of claims 1-4 and 7-33, or a pharmaceutically acceptable salt thereof, wherein R^4 is a C_{3-6} cycloalkyl or $-(C_{1-3} \text{ alkylene})-(C_{3-6} \text{ cycloalkyl})$, wherein each of the C_{3-6} cycloalkyl is optionally substituted with one or more substituents each independently deuterium, halogen, OH, oxo, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.
36. The compound of any of claims 1-4 and 7-31, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 , together with the carbon atom they are both attached to, are joined to form a 3-7 membered carbocyclic ring, such as cyclopropyl or cyclobutyl ring, which is optionally substituted.
37. The compound of any of claims 1-4 and 7-31, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 , together with the carbon atom they are both attached to, are joined to form a 4-8 membered heterocyclic ring having 1 or 2 ring heteroatoms independently selected from O, N, and S, wherein the sulfur atom, if present, is optionally oxidized, and the 4-8 membered heterocyclic ring is optionally substituted, for example, R^3 and R^4 , together with the carbon atom they are both attached to, are joined



38. The compound of any of claims 1-4 and 7-31, or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 , together with the carbon atom they are both attached to, are joined to form an optionally substituted cyclopropyl ring, for example, an unsubstituted



39. The compound of any of claims 1-38, or a pharmaceutically acceptable salt thereof, wherein L^1 is null.

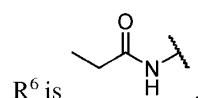
40. The compound of any of claims 1-39, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or C_{1-4} alkyl optionally substituted with F (e.g., methyl, or fluorine substituted methyl), preferably R^5 is hydrogen.
41. The compound of any of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein R^6 is $N(G^{2A})C(O)G^{2B}$, $N(G^{2A})C(O)OG^{2B}$, $N(G^{2A})C(O)NG^{2A}G^{2B}$, $N(G^{2A})SO_2G^{2B}$, or $N(G^{2A})SO_2NG^{2A}G^{2B}$, wherein G^{2A} at each occurrence is independently hydrogen or an optionally substituted C_{1-6} alkyl; and G^{2B} is R^{X1} , $(C_{1-4} \text{ alkylene})-R^{X1}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X1}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, wherein R^{X1} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C_{3-8} carbocyclic ring, optionally substituted 5- or 6-membered heteroaryl ring, or optionally substituted 4-8 membered heterocyclic ring), wherein, when substituted, the optionally substituted group of G^{2A} or R^{X1} is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.
42. The compound of claim 41, or a pharmaceutically acceptable salt thereof, wherein G^{2A} at each occurrence is independently hydrogen or a C_{1-4} alkyl optionally substituted with one or more G^{S2} , wherein G^{S2} at each occurrence is independently deuterium, F, or OH.
43. The compound of claim 41 or 42, or a pharmaceutically acceptable salt thereof, wherein G^{2B} is C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally

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substituted with one or more G^{S1} , or 3-10 membered ring (e.g., carbocyclic, heterocyclic, or heteroaryl ring) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

44. The compound of any of claims 1-40, or a pharmaceutically acceptable salt thereof, wherein R^6 is $NHC(O)G^{2C}$, $NHC(O)OG^{2C}$, or $NHC(O)NHG^{2C}$, and G^{2C} is C_{1-4} alkyl (e.g., methyl or ethyl) optionally substituted with one or more G^{S1} , C_{3-6} cycloalkyl (e.g., cyclobutyl) optionally substituted with one or more G^{S3} , 4-7 membered heterocyclic ring (e.g., oxetanyl) optionally substituted with one or more G^{S3} , or a 5 or 6 membered heteroaryl optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein R^6 is $NHC(O)G^{2D}$, and G^{2D} is (1) C_{1-4} alkyl optionally substituted with one or more deuterium and/or F, or (2) C_{3-6} cycloalkyl optionally substituted with methyl and/or F, for example,



46. The compound of any of claims 1-45, or a pharmaceutically acceptable salt thereof, wherein Y is C(O).
47. The compound of any of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^8 is $NG^{3A}G^{3B}$, wherein G^{3A} is hydrogen or an optionally substituted C_{1-6} alkyl; and

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G^{3B} is R^{X2} , $(C_{1-4} \text{ alkylene})-R^{X2}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X2}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, wherein R^{X2} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C_{3-8} carbocyclic ring, or optionally substituted 4-8 membered heterocyclic ring), wherein, when substituted, the optionally substituted group of G^{3A} or R^{X2} is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

48. The compound of any of claims 1-46, or a pharmaceutically acceptable salt thereof, wherein R^8 is an optionally substituted 4-8 membered heterocyclic ring having 1-3 ring heteroatoms, with one of the ring heteroatoms being a ring nitrogen, which is bonded to Y, and any remaining ring heteroatom(s) being independently selected from N, O, and S, wherein the sulfur atom, if present, is optionally oxidized.
49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^8 has

a structure represented by M-1,  (M-1), which is an optionally substituted ring selected from azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine 1,1,dioxide, and azaspiro[3,3]heptane,

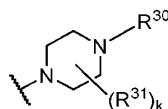
wherein, when substituted, the optionally substituted ring is preferably substituted with one or more substituents each independently deuterium, halogen, OH, oxo (as applicable), CN, R^{X3} , OR^{X3} , $C(O)R^{X3}$, SO_2R^{X3} , $(C_{1-4} \text{ alkylene})-R^{X3}$, or $(C_{1-4} \text{ heteroalkylene})-R^{X3}$, wherein the C_{1-4} heteroalkylene is optionally substituted with oxo, and contains 1-3 heteroatoms

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independently selected from S, O, or N, wherein the S atom, if present, is optionally oxidized, or two substituents together with the atoms they are bonded to are joined to form a 3-6 membered ring, which can be a spiro, fused, or bridged ring,

wherein R^{X3} at each occurrence is independently C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.

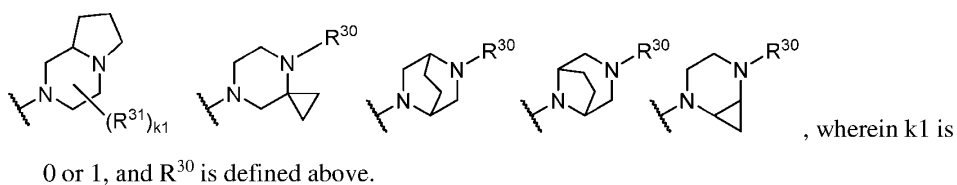
50. The compound of any of claims 1-46, or a pharmaceutically acceptable salt thereof,



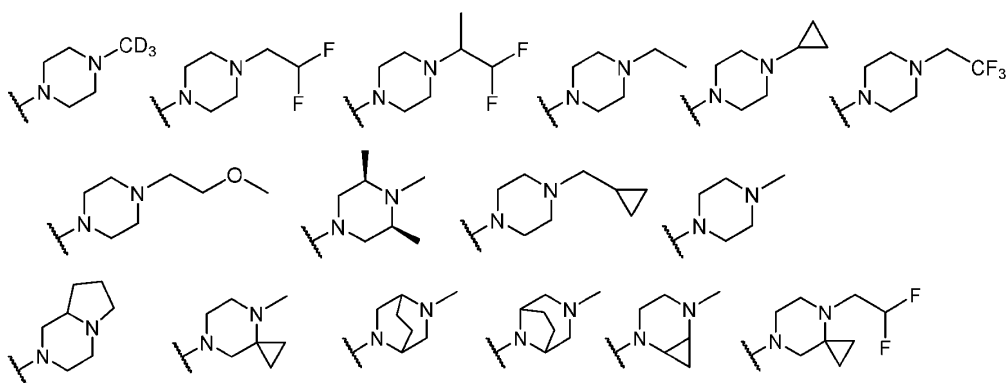
wherein R^8 has a structure represented by M-2,

wherein R^{30} is hydrogen, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} , or $(C_{1-2}$ alkylene)-(3-6 membered ring), wherein the 3-6 membered ring (e.g., cyclopropyl) is optionally substituted with one or more G^{S3} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, k is 0, 1, or 2, and

R^{31} at each occurrence is independently deuterium, oxo, or C_{1-4} alkyl optionally substituted with F, or two R^{31} , together with the intervening atom(s) are joined to form a ring, e.g., a fused or spiro cyclopropyl, or a bridged ring, or one R^{31} and R^{30} , together with the intervening atom(s) are joined to form a ring, for example, R^8 can have a structure selected from:



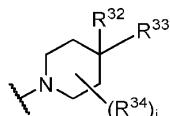
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein R³⁰ is hydrogen or C₁₋₄ alkyl optionally substituted with one or more G^{S1}, or R³⁰ is cyclopropyl or (C₁₋₂ alkylene)-(cyclopropyl), wherein the cyclopropyl is optionally substituted with one or more G^{S1}, wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F, e.g., R³⁰ is CH₃, CD₃, ethyl optionally substituted with 1-3 F (e.g., CH₂CF₂H, CH₂CF₃, etc.), methoxyethyl, cyclopropylmethyl, cyclopropyl, etc., for example, R⁸ can have a structure selected from:



52. The compound of claim 50 or 51, or a pharmaceutically acceptable salt thereof, wherein k is 0.
53. The compound of claim 50 or 51, or a pharmaceutically acceptable salt thereof, wherein k is 1 or 2, and R³¹ at each occurrence is methyl.

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54. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein R^8 has



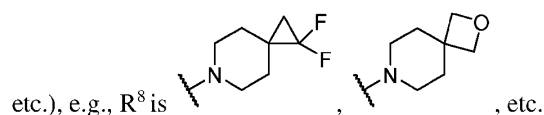
a structure represented by M-3, (M-3),

wherein

R^{32} is hydrogen, halogen, CN, C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} ,

R^{33} is hydrogen, halogen, CN, OH, NH_2 , C_{1-4} alkyl optionally substituted with one or more G^{S1} , C_{1-4} heteroalkyl (e.g., C_{1-4} alkoxy, C_{1-4} monoalkyl amine, or C_{2-4} dialkyl amine) optionally substituted with one or more G^{S1} , or 3-6 membered ring (e.g., cyclopropyl, phenyl, etc.) optionally substituted with one or more G^{S3} ,

or R^{32} and R^{33} , together with the carbon they are both attached to, are joined to form $C(=O)$ or an optionally substituted 3-6 membered ring (e.g., cyclopropyl, cyclobutyl, oxetane,



etc.), e.g., R^8 is , etc.
 wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F; and G^{S3} at each occurrence is independently deuterium, F, OH, C_{1-4} alkyl optionally substituted with deuterium and/or F, or C_{1-4} alkoxy optionally substituted with deuterium and/or F,

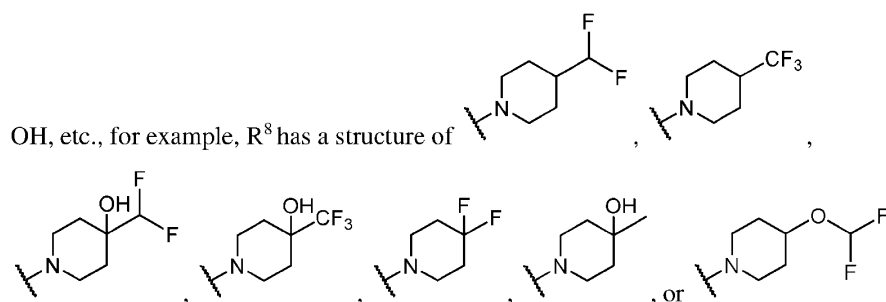
j is 0, 1, or 2, and

R^{34} at each occurrence is independently oxo, deuterium, halogen, CN, C_{1-4} alkyl optionally substituted with F, or two R^{34} , or one R^{34} and one of R^{32} and R^{33} , together with the intervening atom(s) are joined to form a ring, e.g., a spiro cyclopropyl, or a fused or bridged ring.

55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein R^{32} is hydrogen, F, C_{1-4} alkyl optionally substituted with one or more G^{S1} , or C_{1-4} alkoxy optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, e.g., R^{32} is F, CH_3 , CHF_2 , CF_3 , difluoromethoxy, etc.

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56. The compound of claim 54 or 55, or a pharmaceutically acceptable salt thereof, wherein R^{33} is hydrogen, OH, halogen (e.g., F), CN, or C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F, e.g., R^{33} is hydrogen, F, CH_3 ,



57. The compound of any of claims 54-56, or a pharmaceutically acceptable salt thereof, wherein j is 0.
58. The compound of any of claims 54-56, or a pharmaceutically acceptable salt thereof, wherein j is 1 or 2, and R^{34} at each occurrence is independently OH, halogen, CN, or C_{1-4} alkyl optionally substituted with one or more G^{S1} , wherein G^{S1} at each occurrence is independently deuterium, F, OH, or C_{1-4} alkoxy optionally substituted with deuterium and/or F.
59. The compound of any of claims 1-58, or a pharmaceutically acceptable salt thereof, wherein n is 0, 1 or 2, preferably, n is 0 or 1.
60. The compound of any of claims 1-59, or a pharmaceutically acceptable salt thereof, wherein R^7 at each occurrence is independently halogen (e.g., F, Cl, or Br), CN, C_{1-6} alkyl optionally substituted with F, C_{2-6} alkenyl optionally substituted with F, C_{2-6} alkynyl optionally substituted with F, C_{1-6} heteroalkyl optionally substituted with F, optionally substituted 3-7 membered carbocyclic or 4-7 membered heterocyclic ring having 1-2 ring heteroatoms, OG^4 , NG^4G^4 , SG^4 , $C(O)G^4$, or $C(O)NG^4G^4$, wherein G^4 at each occurrence is independently hydrogen, C_{1-6} alkyl optionally substituted with F, or optionally substituted 3-7 membered carbocyclic or heterocyclic ring having 1-2 ring

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heteroatoms, wherein each of the optionally substituted 3-7 membered carbocyclic or heterocyclic ring is optionally substituted with one or more substituents independently selected from deuterium, F, OH, C₁₋₄ alkyl optionally substituted with deuterium and/or F, or C₁₋₄ alkoxy optionally substituted with deuterium and/or F.

61. The compound of any of claims 1-59, or a pharmaceutically acceptable salt thereof, wherein R⁷ at each occurrence is independently F, Cl, C₁₋₄ alkyl optionally substituted with F, C₂₋₄ alkenyl optionally substituted with F, C₂₋₄ alkynyl optionally substituted with F, or C₁₋₄ heteroalkyl optionally substituted with F.
62. A compound selected from Table 1, or Examples 1-174, or a pharmaceutically acceptable salt thereof.
63. A pharmaceutical composition comprising the compound of any of claims 1-62, or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.
64. A method of modulating IL-17A and/or IL-17F in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any of claims 1-62, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 63.
65. A method of treating an inflammatory disease or condition in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any of claims 1-62, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 63.
66. The method of claim 65, wherein the inflammatory disease or condition is selected from plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, rheumatoid arthritis, Palmoplantar Psoriasis, Spondyloarthritis, and Non-infectious Uveitis.