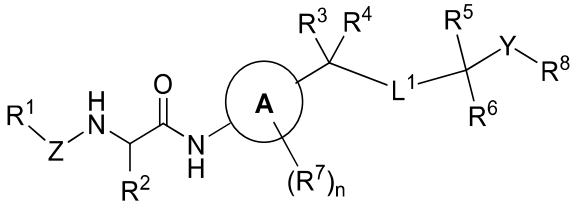
(*e.g.*, secukinumab and ixekizumab) as well as an antibody against IL-17 receptors (*e.g.*, brodalumab) have been approved by the U.S. Food and Drug Administration for treating patients with autoimmune disorders (*e.g.*, Ps, PsA, and AS). Despite these advancements, small molecule modulators of IL-17 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.

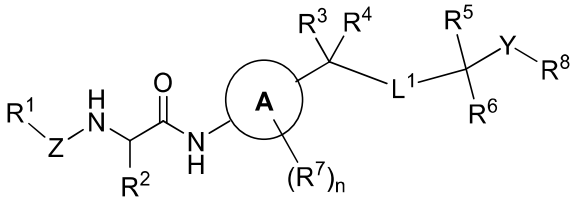
[0005] In some embodiments, the present disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



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.

[0005a] In one aspect, there is provided a compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein **R^1** is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} 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 C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-8 membered ring; **R^2** 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 R^7 as valency permits; **R^3 and R^4** are each independently F, CN, G^{1A}, or J^1-J^2-J^3-G^{1B}, wherein J^1, J^2, and J^3 are each independently null, O, NG^{1B}, C(O), S, SO, SO_2, or P(O)G^{1B}, provided that at least one of J^1, J^2, and J^3 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 C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-8 membered ring; or **R^3 and R^4**, 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; **L^1** is null, an optionally substituted C_{1-4} alkylene, or an optionally substituted C_{1-4} heteroalkylene, **R^5** is hydrogen, deuterium, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or optionally substituted 3-8 membered ring; or either **R^3 or 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; **R^6** is O-G^{2A}, N(G^{2A})C(O)G^{2A}, N(G^{2A})C(O)OG^{2B}, N(G^{2A})C(O)N$G^{2A}G^{2A}$, N(G^{2A})SO_2G^{2B}, or N(G^{2A})$SO_2NG^{2A}G^{2A}$, wherein G^{2A} at each occurrence is independently hydrogen or G^{2B}; and wherein G^{2B} at each occurrence is independently an optionally substituted 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), **Y** is C(O) or SO_2; $\mathbf{R^8}$ is NG^3G^3, an optionally substituted 4-14 membered heterocyclic ring, or an optionally substituted heteroaryl ring, wherein: G^3 at each occurrence is independently hydrogen, 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 3-8 membered ring; or two G^3, together with the nitrogen atom they are both attached to, are joined to form an optionally substituted 4-8 membered heterocyclic ring; $\mathbf{R^7}$ at each occurrence is independently deuterium, halogen, CN, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, optionally substituted 3-8 membered ring, or J^4-J^5-J^6-G^4, wherein J^4, J^5, and J^6 are each independently null, O, NG^4, C(O), S, SO, SO_2, or $P(O)G^4$, wherein at least one of J^4, J^5, and J^6 is not null, and wherein G^4 at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} 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

[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

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

[0006a] In another aspect, there is provided a pharmaceutical composition comprising the compound as described herein, or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.

[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.

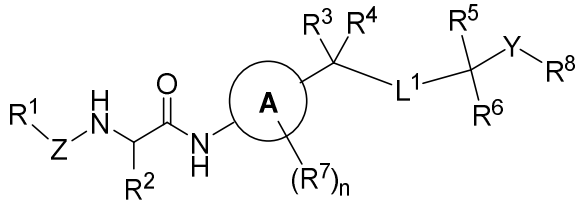
[0008a] In yet another aspect, the present disclosure provides a use of the compound described herein or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating an inflammatory disease or condition in a subject in need thereof.

[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

WHAT IS CLAIMED IS:

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



Formula I

wherein:

R^1 is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} 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 C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-8 membered ring;

R^2 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 R^7 as valency permits;

R^3 and R^4 are each independently F, CN, G^{1A}, or J^1-J^2-J^3-G^{1B}, wherein J^1, J^2, and J^3 are each independently null, O, NG^{1B}, C(O), S, SO, SO_2, or P(O)G^{1B}, provided that at least one of J^1, J^2, and J^3 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 C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-8 membered ring;

or **R^3 and R^4**, 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;

L^1 is null, an optionally substituted C_{1-4} alkylene, or an optionally substituted C_{1-4} heteroalkylene,

R^5 is hydrogen, deuterium, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, or optionally substituted 3-8 membered ring;

or either **R^3 or 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;

R^6 is O-G^{2A}, N(G^{2A})C(O)G^{2A}, N(G^{2A})C(O)OG^{2B}, N(G^{2A})C(O)N$G^{2A}G^{2A}$, N(G^{2A})SO_2G^{2B}, or N(G^{2A})SO_2N$G^{2A}G^{2A}$, wherein G^{2A} at each occurrence is independently hydrogen or G^{2B}; and wherein G^{2B} at each occurrence is independently an optionally substituted 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),

Y is C(O) or SO_2;

R^8 is NG^3G^3, an optionally substituted 4-14 membered heterocyclic ring, or an optionally substituted heteroaryl ring, wherein:

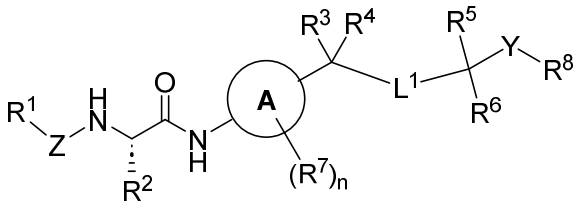
G^3 at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-8 membered ring; or two G^3, together with the nitrogen atom they are both attached to, are joined to form an optionally substituted 4-8 membered heterocyclic ring;

R^7 at each occurrence is independently deuterium, halogen, CN, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, optionally substituted 3-8 membered ring, or J^4-J^5-J^6-G^4, wherein J^4, J^5, and J^6 are each independently null, O, NG^4, C(O), S, SO, SO_2, or P(O)G^4, wherein at least one of J^4, J^5, and J^6 is not null, and wherein G^4 at each occurrence is independently hydrogen, an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} 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

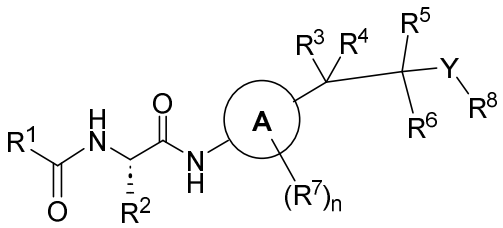
"n" is an integer selected from 0-4.

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



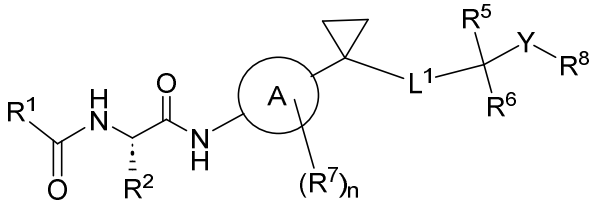
Formula I-E1; or

characterized as having a structure according to Formula I-2:



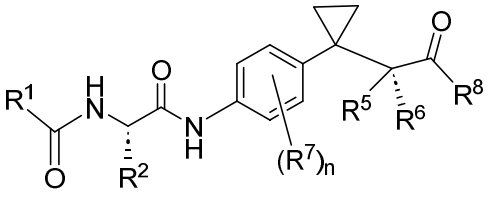
Formula I-2.

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

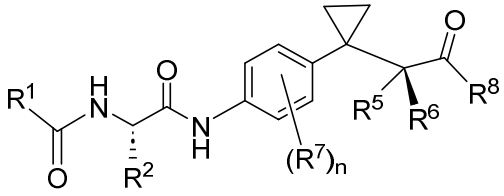


Formula I-3.

4. 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.

5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^1 is an optionally substituted 5- or 6-membered heteroaryl; optionally, 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 with one or more substituents independently selected from halogen, CN, OH, NH_2, R^{A1}, OR^{A1}, SR^{A1}, NHR^{A1}, $NR^{A1}R^{A1}$, $NR^{A1}SO_2R^{A1}$, $C(O)R^{A1}$, $C(O)NHR^{A1}$, $C(O)NR^{A1}R^{A1}$, $S(O)_qR^{A1}$, $S(O)_qNR^{A1}R^{A1}$, and $S(O)(=NR^{A1})R^{A1}$,

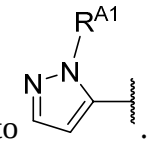
wherein

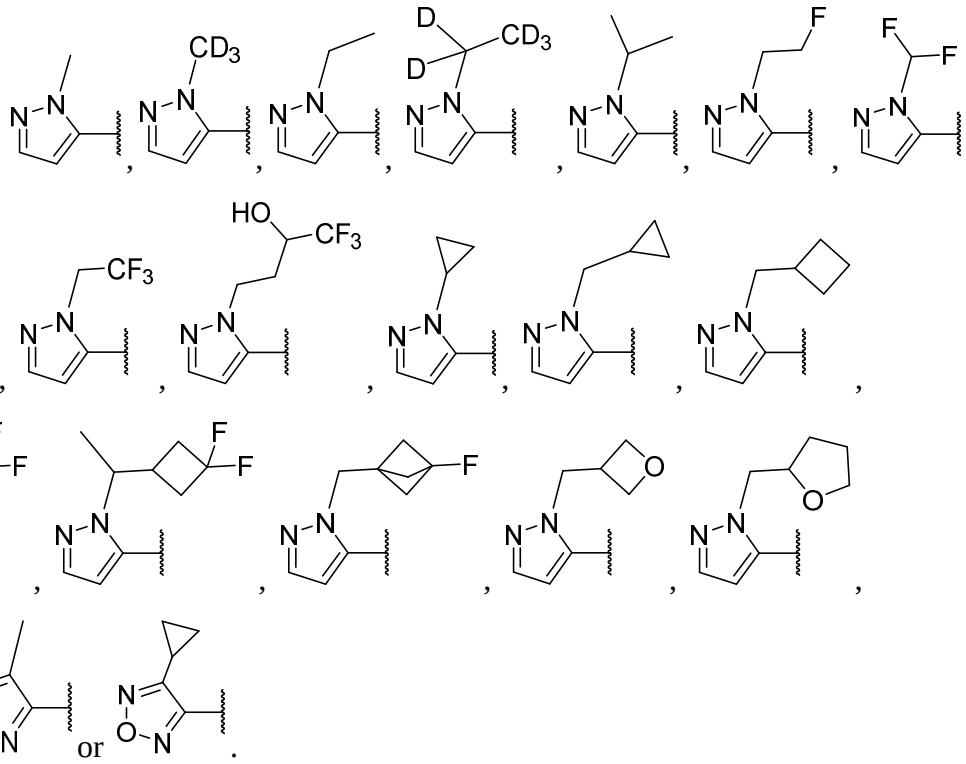
q is 1 or 2; and

R^{A1} at each occurrence is independently C_{1-6} alkyl, C_{3-10} carbocyclic, or 4-10 membered heterocyclic ring, wherein:

the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring (e.g., cyclopropyl, cyclobutyl, etc.), 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 C_{3-10} carbocyclic or 4-10 membered heterocyclic ring is optionally 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.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^1 has a structure according to .

7. The compound of any of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^1 is .

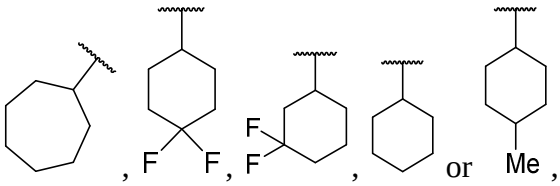
8. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^2 is an optionally substituted 3-14 membered carbocyclyl, which is monocyclic or polycyclic, and wherein when substituted, the 3-14 membered carbocyclyl is substituted with one or more substituents each independently 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},

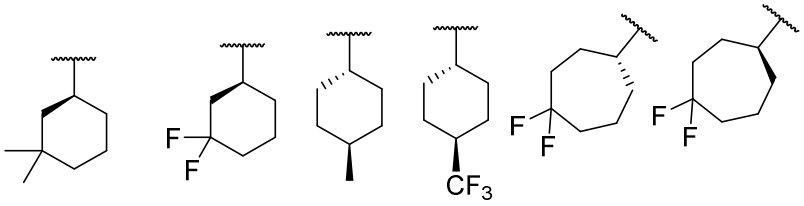
wherein R^{A2} at each occurrence is independently hydrogen or R^{B2}, and

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,

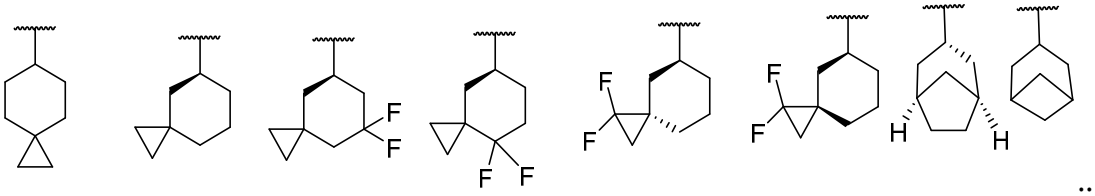
the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} heteroalkyl and 3-8 membered ring are optionally substituted with one or more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

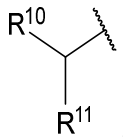
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^2 is , or R^2 is selected from:

; or

R^2 is selected from:

..

10. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof,

wherein R^2 has a structure of , wherein

R^{10} and R^{11} are each independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted C_{3-7} carbocyclic, or optionally substituted phenyl, wherein at least one of R^{10} and R^{11} is not hydrogen.

11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein R^{10} is (1) a C_{3-6} cycloalkyl; or (2) –(C_{1-3} alkylene)-(C_{3-6} 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^{10} is cyclopropyl, methylcyclopropyl, or cyclobutyl; and wherein R^{11} is (1) a C_{3-6} cycloalkyl; or (2) –(C_{1-3} alkylene)-(C_{3-6} 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.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{10} and R^{11} are both cyclopropyl, cyclobutyl, or phenyl.

13. The compound of any of claims 1-7, 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 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,

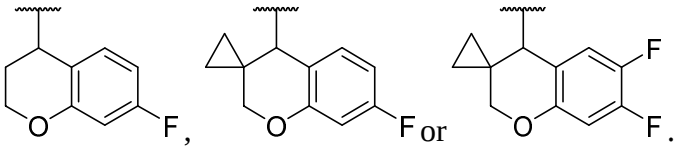
the C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl is substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} heteroalkyl and 3-8 membered ring are optionally substituted with one or more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

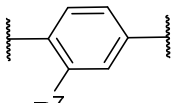
the 3-7 membered carbocyclic or 4-7 membered heterocyclic ring is substituted with one or more substituents independently selected from deuterium, halogen, OH, CN, C_{1-6} alkyl, C_{1-6} heteroalkyl, oxo, and 3-8 membered ring, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl and 3-8 membered ring are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

optionally,

wherein the optionally substituted 10-14 membered polycyclic heterocyclyl 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, 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; optionally, 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, and optionally, the optionally substituted 10-14 membered polycyclic heterocyclyl is



14. The compound of any of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Ring A and $(R^7)_n$ together have a structure of , wherein R^7 is ortho to the amide NH in Formula I.

15. The compound of any of claims 1-3 or 5-14, 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; or
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, which is optionally substituted; or
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.

16. The compound of any of claims 1-3 or 5-14, 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.

17. The compound of any of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or C_{1-4} alkyl optionally substituted with F; and
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} alkylene)-R^{X1}, or (C_{1-4} 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,

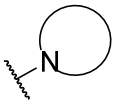
wherein R^{X1} is an optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{3-6} alkynyl, an optionally substituted C_{1-6} heteroalkyl, or optionally substituted 3-14 membered ring (e.g., optionally substituted C_{3-8} carbocyclic ring, optionally substituted 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 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.

18. The compound of any of claims 1-17, 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.

19. The compound of any of claims 1-18, 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.

20. The compound of claim 19, 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 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} alkylene)-R^{X3}, or (C_{1-4} 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.

21. The compound of any of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein 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; and n is 0, 1, or 2.

22. A compound selected from Table 1, or Examples 1-174, or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising the compound of any of claims 1-22, or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable excipient.

24. Use of the compound of any of claims 1-22 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 23 in the manufacture of a medicament for treating an inflammatory disease or condition in a subject in need thereof.