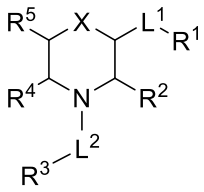
[0010] FIG. 5 shows C5a induced CD11b upregulation on neutrophil was blocked by compound Nos. 47 and 89 on neutrophil in human C5aR knock-in mice whole blood by orally pre-dosing.

[0011] FIG. 6 shows C5a induced CD11b upregulation on neutrophil was blocked by compound Nos. 47 and 49 on neutrophil in human C5aR knock-in mice whole blood by orally pre-dosing.

SUMMARY

[0011a] In an aspect of the present disclosure, there is provided a compound of formula (I),



(I),

or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X is -O- or -CHR^{6}-,

provided that when X is -O-, then L^{1} is *-C(O)NH-** and L^{2} is -C(O)-;

R^{1} is C$_{3-12}$ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C$_{6-14}$ aryl, each of which is independently optionally substituted with one or more R^{11},

wherein each R^{11} is independently oxo, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1b}, -NO$_2$, -C(O)R^{1a}, -OC(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1b}, -OC(O)NR^{1a}R^{1b}, -NR^{1a}C(O)R^{1b}, -NR^{1a}C(O)OR^{1b}, -S(O)R^{1a}, -S(O)$_2$R^{1a}, -NR^{1a}S(O)R^{1b}, -C(O)NR^{1a}S(O)R^{1b}, -NR^{1a}S(O)$_2$R^{1b}, -C(O)NR^{1a}S(O)$_2$R^{1b}, -S(O)NR^{1a}R^{1b}, -S(O)$_2$NR^{1a}R^{1b}, -P(O)R^{1a}R^{1b}, C$_{3-6}$ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C$_{6-14}$ aryl, -(C$_{1-6}$ alkylene) NR^{1a}R^{1b}, -(C$_{1-6}$ alkylene) C$_{3-6}$ cycloalkyl, -(C$_{1-6}$ alkylene) 3- to 12-membered heterocyclyl, -(C$_{1-6}$ alkylene) 5- to 12-membered heteroaryl, or -(C$_{1-6}$ alkylene) C$_{6-14}$ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, halogen, hydroxyl, C$_{1-6}$ alkoxy, and –CN,

wherein R^{1a} and R^{1b} are each independently H, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{3-12}$ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C$_{6-14}$ aryl, or

R^{1a} and R^{1b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

R^2 is C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, or C_{6-14} aryl, each of which is independently optionally substituted with one or more –Q-W, wherein:

Q is C_{1-6} alkylene, –(N-L^3-R^Q)- or –O-,

wherein R^Q is H, C_{1-6} alkyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, and

L^3 is –C(O)-, *-C(O)O-CH_2-**, or a bond, wherein * indicates the point of attachment to N and ** indicates the point of attachement to R^Q, W is H, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, each of which is independently optionally substituted with one or more R^7;

R^3 is H, C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, wherein the C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, and C_{6-14} aryl are each independently optionally substituted with one or more R^{31},

wherein each R^{31} is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{3a}, -SR^{3a}, -$NR^{3a}R^{3b}$, -NO_2, -$C(O)R^{3a}$, -$OC(O)R^{3a}$, -$C(O)OR^{3a}$, -$C(O)NR^{3a}R^{3b}$, -$OC(O)NR^{3a}R^{3b}$, -$NR^{3a}C(O)R^{3b}$, -$NR^{3a}C(O)OR^{3b}$, -$S(O)R^{3a}$, -$S(O)_2R^{3a}$, -$NR^{3a}S(O)R^{3b}$, -$C(O)NR^{3a}S(O)R^{3b}$, -$NR^{3a}S(O)_2R^{3b}$, -$C(O)NR^{3a}S(O)_2R^{3b}$, -$S(O)NR^{3a}R^{3b}$, -$S(O)_2NR^{3a}R^{3b}$, -$P(O)R^{3a}R^{3b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{3a}R^{3b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN,

wherein R^{3a} and R^{3b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{3a} and R^{3b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN; and

R^4, R^5, and R^6 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, hydroxyl, C_{1-6} alkoxy,C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and C_{6-14} aryl are each independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, and wherein,

R^4 and R^5 or R^5 and R^6 may be taken together with the carbon atoms to which they are attached to form a ring B which is independently optionally substituted with one or more R^8, wherein ring B is C_{3-12} cycloalkyl or 3- to 12- membered heterocyclyl, and

R^4 may be taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L^2, and part of R^3 to form a 6- to 8- membered heterocyclyl;

each R^7 is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{7a}, -SR^{7a}, -$NR^{7a}R^{7b}$, -NO_2, -$C(O)R^{7a}$, -$OC(O)R^{7a}$, -$C(O)OR^{7a}$, -$C(O)NR^{7a}R^{7b}$, -$OC(O)NR^{7a}R^{7b}$, -$NR^{7a}C(O)R^{7b}$, -$NR^{7a}C(O)OR^{7b}$, -$S(O)R^{7a}$, -$S(O)_2R^{7a}$, -$NR^{7a}S(O)R^{7b}$, -$C(O)NR^{7a}S(O)R^{7b}$, -$NR^{7a}S(O)_2R^{7b}$, -$C(O)NR^{7a}S(O)_2R^{7b}$, -$S(O)NR^{7a}R^{7b}$, -$S(O)_2NR^{7a}R^{7b}$, -$P(O)R^{7a}R^{7b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{7a}R^{7b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, wherein

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{7a} and R^{7b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

each R^8 is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{8a}, -SR^{8a}, -$NR^{8a}R^{8b}$, -NO_2, -$C(O)R^{8a}$, -$OC(O)R^{8a}$, -$C(O)OR^{8a}$, -$C(O)NR^{8a}R^{8b}$, -$OC(O)NR^{8a}R^{8b}$, -$NR^{8a}C(O)R^{8b}$, -$NR^{8a}C(O)OR^{8b}$, -$S(O)R^{8a}$, -$S(O)_2R^{8a}$, -$NR^{8a}S(O)R^{8b}$, -$C(O)NR^{8a}S(O)R^{8b}$, -$NR^{8a}S(O)_2R^{8b}$, -$C(O)NR^{8a}S(O)_2R^{8b}$, -$S(O)NR^{8a}R^{8b}$, -$S(O)_2NR^{8a}R^{8b}$, -$P(O)R^{8a}R^{8b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{8a}R^{8b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, wherein

R^{8a} and R^{8b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{8a} and R^{8b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

L^1 is *-C(O)NH-**, a bond, -C(O)-, *-CH_2-NH-**, or *-C(O)NH-CH_2-**, wherein * indicates the point of attachment to the carbon atom of the piperidine and ** indicates the point of attachment to R^1;

L^2 is –C(O)-, a bond, -CH_2-, -$S(O)_2$-, or #-$S(O)_2$-CH_2-##, wherein # indicates the point of attachment to the nitrogen atom and ## indicates the point of attachment to R^3,

provided that when X is -CHR^6- and R^4, R^5, and R^6 are all H, then at least one of the following conditions apply:

(1) L^1 is a bond, -C(O)-, *-CH_2-NH-**, or *-C(O)NH-CH_2-**,

(2) L^2 is a bond, -CH_2-, -$S(O)_2$-, or #-$S(O)_2$-CH_2-##, and

(3) R^2 is phenyl substituted with one or more –Q-W, wherein Q is –(N-L^3-R^Q)- and R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.

[0011b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of the compounds in Table 1, or a pharmaceutically acceptable salt of any of the foregoing.

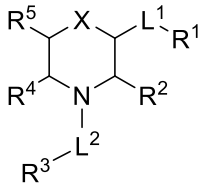
[0011c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

[0011d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for inhibiting C5a receptor.

[0011e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating a disorder mediated by the complement pathways; optionally wherein the disorder is an inflammatory disease, a cardiovascular or cerebrovascular disease, or an autoimmune disease or wherein the disease or disorder is at least selected from the group consisting of: macular degeneration (MD), age-related macular degeneration (AMD), ischemia reperfusion injury, arthritis, rheumatoid arthritis, lupus, ulcerative colitis, stroke, post-surgery systemic inflammatory syndrome, asthma, allergic asthma, chronic obstructive pulmonary disease (COPD), paroxysmal nocturnal hemoglobinuria (PNH) syndrome, autoimmune hemolytic anemia (AIHA), Gaucher disease, myasthenia gravis, neuromyelitis optica, (NMO), multiple sclerosis, delayed graft function, antibody-mediated rejection, atypical hemolytic uremic syndrome (aHUS), central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), epidermolysis bullosa, sepsis, septic shock, organ transplantation, inflammation (including, but not limited to, inflammation associated with cardiopulmonary bypass surgery and kidney dialysis), C3 glomerulopathy, membranous nephropathy, IgA nephropathy, glomerulonephritis (including, but not limited to, anti-neutrophil cytoplasmic antibody (ANCA)-mediated glomerulonephritis, lupus nephritis, and combinations thereof), ANCA-mediated vasculitis, Shiga toxin induced HUS, and antiphospholipid antibody-induced pregnancy loss, graft versus host disease (GVHD), bullous pemphigoid, hidradenitis suppurativa, dermatitis herpetiformis, sweets syndrome, pyoderma gangrenosum, palmo-plantar pustulosis & pustular psoriasis, rheumatoid neutrophilic dermatoses, subcorneal pustular dermatosis, bowel-associated dermatosis-arthritis syndrome, neutrophilic eccrine hidradenitis, linear IgA disease, or any combinations thereof.

[0011f] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, for use in therapy.

[0012] In one example, provided is a compound of formula (I):



(I),

or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1, R^2, R^3, R^4, R^5, X, L^1, and L^2 are as disclosed herein.

[0013] In another example, provided is a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier or excipient. Also provided is a kit comprising a compound as described herein.

[0014] In another example, provided is a method of treating a C5a-mediated disorder in an individual in need thereof, comprising administering an therapeutically effective amount of a compound as described herein, or pharmaceutically acceptable salt thereof, to the individual. Also provided is use of a compound as described herein, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a C5a-mediated disease.

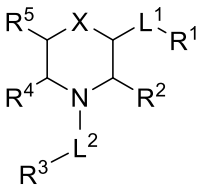
DETAILED DESCRIPTION

[0015] The following description sets forth exemplary embodiments of the present disclosure. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

Definitions

CLAIMS

1. A compound of formula (I),



(I),

or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X is -O- or -CHR^6-,

provided that when X is -O-, then L^1 is *-C(O)NH-** and L^2 is -C(O)-;

R^1 is C$_{3-12}$ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C$_{6-14}$ aryl, each of which is independently optionally substituted with one or more R^{11},

wherein each R^{11} is independently oxo, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1b}, -NO$_2$, -C(O)R^{1a}, -OC(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1b}, -OC(O)NR^{1a}R^{1b}, -NR^{1a}C(O)R^{1b}, -NR^{1a}C(O)OR^{1b}, -S(O)R^{1a}, -S(O)$_2$R^{1a}, -NR^{1a}S(O)R^{1b}, -C(O)NR^{1a}S(O)R^{1b}, -NR^{1a}S(O)$_2$R^{1b}, -C(O)NR^{1a}S(O)$_2$R^{1b}, -S(O)NR^{1a}R^{1b}, -S(O)$_2$NR^{1a}R^{1b}, -P(O)R^{1a}R^{1b}, C$_{3-6}$ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C$_{6-14}$ aryl, -(C$_{1-6}$ alkylene) NR^{1a}R^{1b}, -(C$_{1-6}$ alkylene) C$_{3-6}$ cycloalkyl, -(C$_{1-6}$ alkylene) 3- to 12-membered heterocyclyl, -(C$_{1-6}$ alkylene) 5- to 12-membered heteroaryl, or -(C$_{1-6}$ alkylene) C$_{6-14}$ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, halogen, hydroxyl, C$_{1-6}$ alkoxy, and –CN,

wherein R^{1a} and R^{1b} are each independently H, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, C$_{3-12}$ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C$_{6-14}$ aryl, or

R^{1a} and R^{1b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, halogen, hydroxyl, C$_{1-6}$ alkoxy, and -CN;

R^2 is C$_{3-12}$ cycloalkyl, 3- to 12- membered heterocyclyl, or C$_{6-14}$ aryl, each of which is independently optionally substituted with one or more –Q-W, wherein:

Q is C_{1-6} alkylene, –(N-L^3-R^Q)- or –O-,

wherein R^Q is H, C_{1-6} alkyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, and

L^3 is –C(O)-, *-C(O)O-CH_2-**, or a bond, wherein * indicates the point of attachment to N and ** indicates the point of attachement to R^Q, W is H, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, each of which is independently optionally substituted with one or more R^7;

R^3 is H, C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, wherein the C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, and C_{6-14} aryl are each independently optionally substituted with one or more R^{31},

wherein each R^{31} is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{3a}, -SR^{3a}, -$NR^{3a}R^{3b}$, -NO_2, -C(O)R^{3a}, -OC(O)R^{3a}, -C(O)OR^{3a}, -C(O)$NR^{3a}R^{3b}$, -OC(O)$NR^{3a}R^{3b}$, -NR^{3a}C(O)R^{3b}, -NR^{3a}C(O)OR^{3b}, -S(O)R^{3a}, -$S(O)_2R^{3a}$, -NR^{3a}S(O)R^{3b}, -C(O)NR^{3a}S(O)R^{3b}, -$NR^{3a}$$S(O)_2R^{3b}$, -C(O)$NR^{3a}$$S(O)_2R^{3b}$, -S(O)$NR^{3a}R^{3b}$, -$S(O)_2NR^{3a}R^{3b}$, -P(O)$R^{3a}R^{3b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{3a}R^{3b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN,

wherein R^{3a} and R^{3b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{3a} and R^{3b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN; and

R^4, R^5, and R^6 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, hydroxyl, C_{1-6} alkoxy,C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and C_{6-14} aryl are each independently optionally substituted with one or more substituents selected from the

group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, and wherein,

R^4 and R^5 or R^5 and R^6 may be taken together with the carbon atoms to which they are attached to form a ring B which is independently optionally substituted with one or more R^8, wherein ring B is C_{3-12} cycloalkyl or 3- to 12- membered heterocyclyl, and

R^4 may be taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L^2, and part of R^3 to form a 6- to 8- membered heterocyclyl;

each R^7 is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{7a}, -SR^{7a}, -$NR^{7a}R^{7b}$, -NO_2, -$C(O)R^{7a}$, -$OC(O)R^{7a}$, -$C(O)OR^{7a}$, -$C(O)NR^{7a}R^{7b}$, -$OC(O)NR^{7a}R^{7b}$, -$NR^{7a}C(O)R^{7b}$, -$NR^{7a}C(O)OR^{7b}$, -$S(O)R^{7a}$, -$S(O)_2R^{7a}$, -$NR^{7a}S(O)R^{7b}$, -$C(O)NR^{7a}S(O)R^{7b}$, -$NR^{7a}S(O)_2R^{7b}$, -$C(O)NR^{7a}S(O)_2R^{7b}$, -$S(O)NR^{7a}R^{7b}$, -$S(O)_2NR^{7a}R^{7b}$, -$P(O)R^{7a}R^{7b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{7a}R^{7b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, wherein

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{7a} and R^{7b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

each R^8 is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OR^{8a}, -SR^{8a}, -$NR^{8a}R^{8b}$, -NO_2, -$C(O)R^{8a}$, -$OC(O)R^{8a}$, -$C(O)OR^{8a}$, -$C(O)NR^{8a}R^{8b}$, -$OC(O)NR^{8a}R^{8b}$, -$NR^{8a}C(O)R^{8b}$, -$NR^{8a}C(O)OR^{8b}$, -$S(O)R^{8a}$, -$S(O)_2R^{8a}$, -$NR^{8a}S(O)R^{8b}$, -$C(O)NR^{8a}S(O)R^{8b}$, -$NR^{8a}S(O)_2R^{8b}$, -$C(O)NR^{8a}S(O)_2R^{8b}$, -$S(O)NR^{8a}R^{8b}$, -$S(O)_2NR^{8a}R^{8b}$, -$P(O)R^{8a}R^{8b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, -(C_{1-6} alkylene) $NR^{8a}R^{8b}$, -(C_{1-6} alkylene)C_{3-6} cycloalkyl, -(C_{1-6} alkylene) 3- to 12-membered heterocyclyl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, or -(C_{1-6} alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents

selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN, wherein

R^{8a} and R^{8b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{8a} and R^{8b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

L^1 is *-C(O)NH-**, a bond, -C(O)-, *-CH_2-NH-**, or *-C(O)NH-CH_2-**, wherein * indicates the point of attachment to the carbon atom of the piperidine and ** indicates the point of attachment to R^1;

L^2 is –C(O)-, a bond, -CH_2-, -$S(O)_2$-, or #-$S(O)_2$-CH_2-##, wherein # indicates the point of attachment to the nitrogen atom and ## indicates the point of attachment to R^3,

provided that when X is -CHR^6- and R^4, R^5, and R^6 are all H, then at least one of the following conditions apply:

(1) L^1 is a bond, -C(O)-, *-CH_2-NH-**, or *-C(O)NH-CH_2-**,

(2) L^2 is a bond, -CH_2-, -$S(O)_2$-, or #-$S(O)_2$-CH_2-##, and

(3) R^2 is phenyl substituted with one or more –Q-W, wherein Q is –(N-L^3-R^Q)- and R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.

2. The compound claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 and R^5 are taken together with the carbon atoms to which they are attached to form a ring B, which is optionally substituted with one or more R^8.

3. The compound of claim 1 or 2, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein either ring B is a C_{3-12} cycloalkyl, which is optionally substituted with one or more R^8; optionally

wherein ring B is cyclopentyl, which is optionally substituted with one or more R^8; or ring B is a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^8,; optionally

wherein the ring B is tetrahydrofuranyl, which is optionally substituted with one or more R^8; or

wherein B is pyrrolidinyl, which is optionally substituted with one or more R^8.

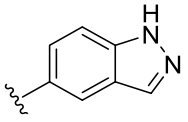
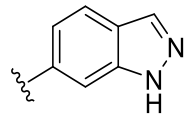
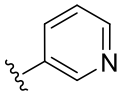
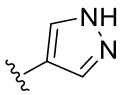
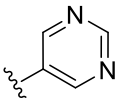
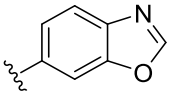
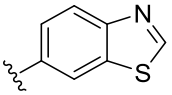
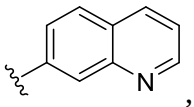
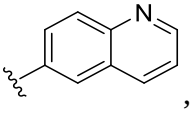
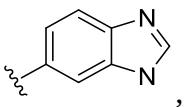
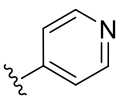
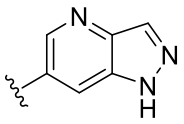
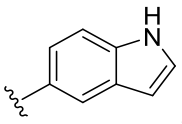
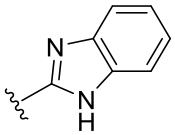
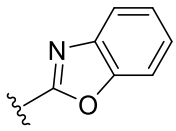
4. The compound of any one of claims 1-3, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^8 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, or $-C(O)R^{8a}$, each of which is independently optionally substituted with one or more halogen.

5. The compound of claims 1-4, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is $-CHR^6-$, wherein R^6 is H.

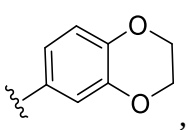
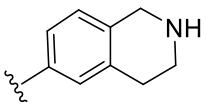
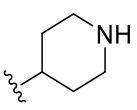
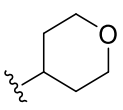
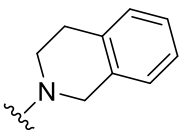
6. The compound of any one of claims 1-5, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein

(a) R^1 is C_{6-14} aryl, which is optionally substituted with one or more R^{11}; optionally wherein R^1 is phenyl, which is optionally substituted with one or more R^{11};

(b) R^1 is 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^{11}; optionally wherein R^1 is selected from the group consisting of:
















, and , each of which is independently optionally substituted with one or more R^{11}; or

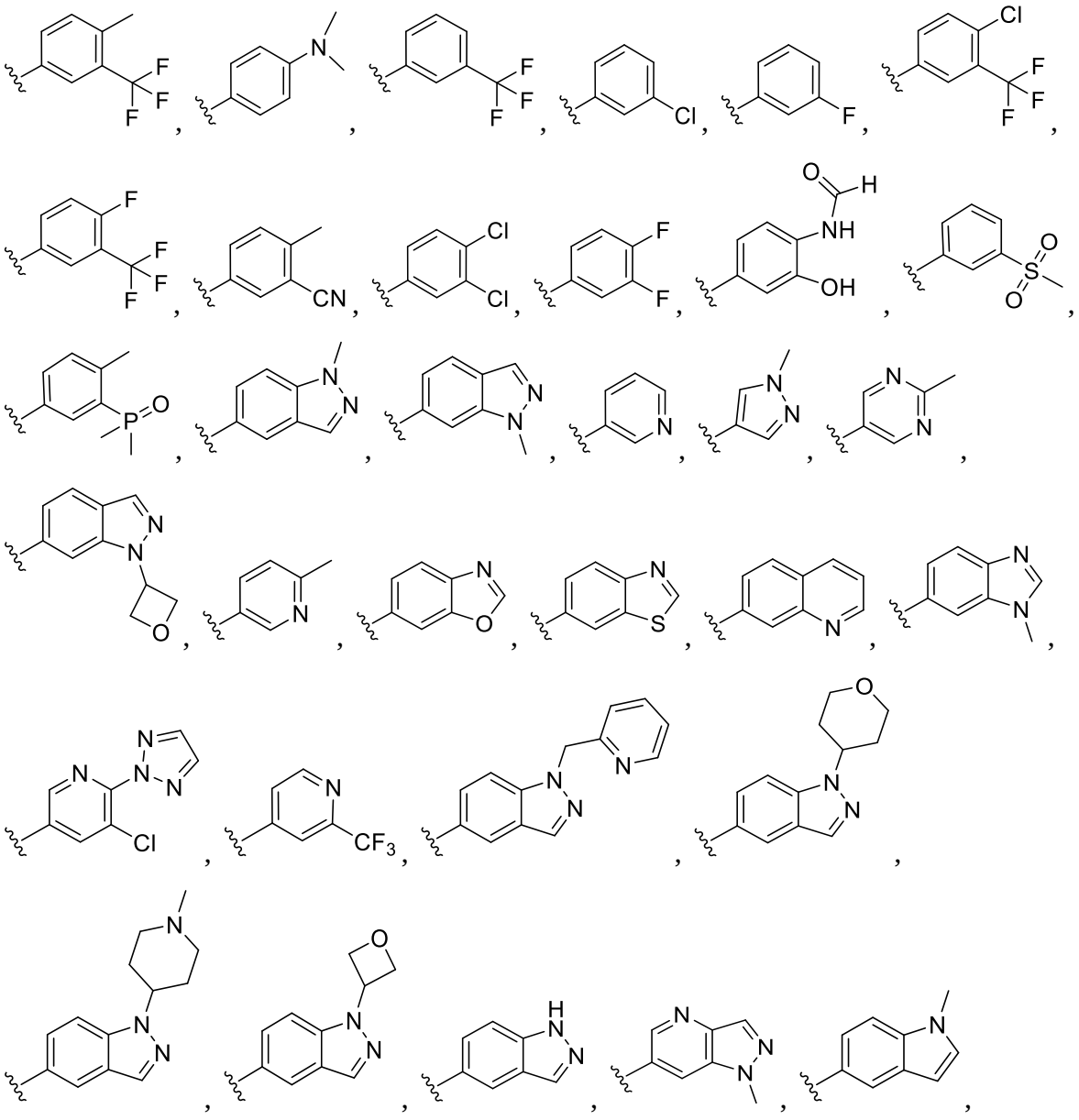
(c) R^1 is 3- to 12- membered heterocyclyl optionally substituted with one or more R^{11}; optionally wherein R^1 is selected from the group consisting of:

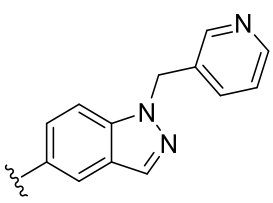
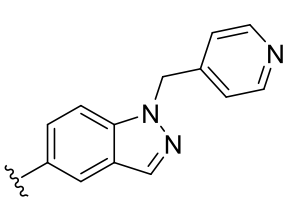
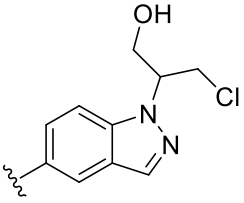
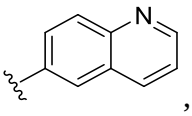
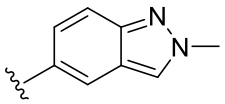
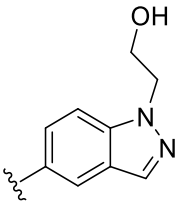
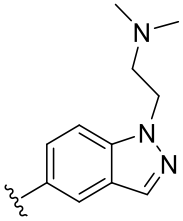
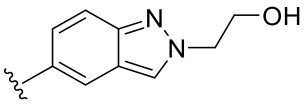
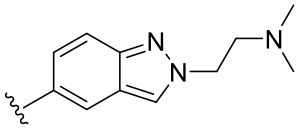
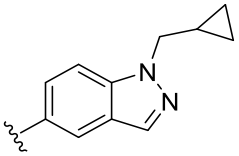
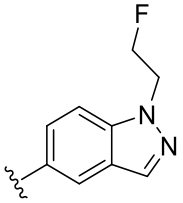
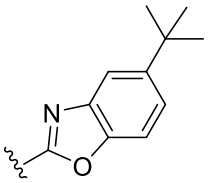
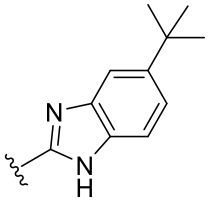
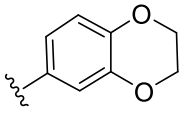
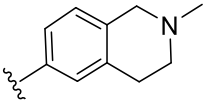
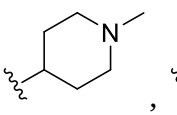
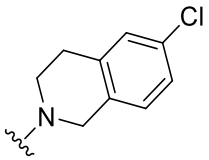




, and, , each of which is independently optionally substituted with one or more R^{11}.

7. The compound of any one of claims 1-6, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{11} is independently C_{1-6} alkyl, $-NR^{1a}R^{1b}$, halogen, -CN, $-OR^{1a}$, $-NR^{1a}C(O)R^{1b}$, $-S(O)_2R^{1a}$, $-P(O)R^{1a}R^{1b}$, 3- to 12-

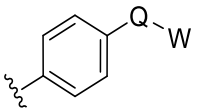
membered heterocyclyl, 5- to 12-membered heteroaryl, -(C_{1-6} alkylene) 5- to 12-membered heteroaryl, -(C_{1-6} alkylene) $NR^{1a}R^{1b}$, or -(C_{1-6} alkylene) C_{3-6} cycloalkyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN.

8. The compound of any one of claims 1-5, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is selected from the group consisting of:




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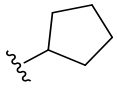
9. The compound of any one of claims 1-8, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{6-14} aryl optionally substituted with one or more –Q-W; optionally wherein R^2 is phenyl optionally substituted with one or more –Q-W.

10. The compound of claim 9, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 
.

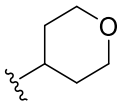
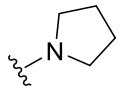
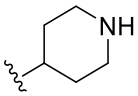
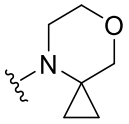
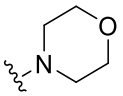
11. The compound of any one of claims 1-10, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is $–(N\text{-}L^3\text{-}R^Q)$-.

12. The compound of claim 11, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^Q is H.

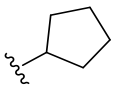
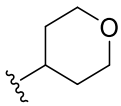
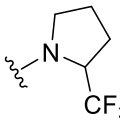
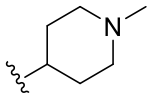
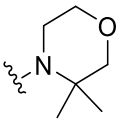
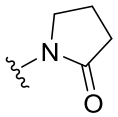
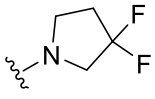
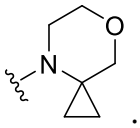
13. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein

(a) W is C_{3-12} cycloalkyl, which is optionally substituted with one or more R^7; optionally wherein W is , which is optionally substituted with one or more R^7; or

(b) W is 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^7; optionally wherein W is selected from the group consisting of:

, , , , and , each of which is independently optionally substituted with one or more R^7.

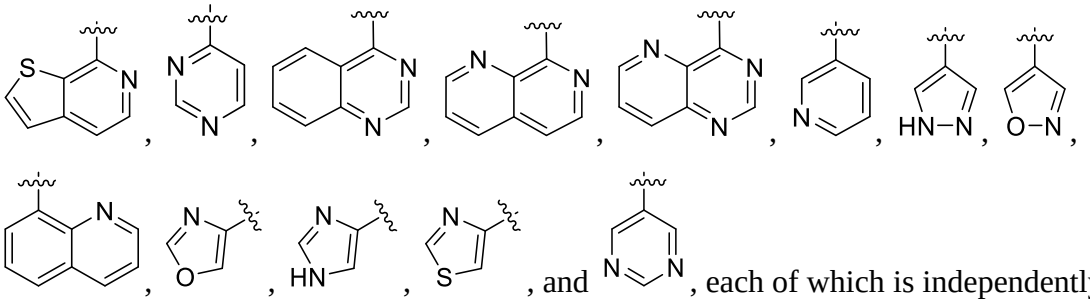
14. The compound of any one of claims 1-13, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^7 is independently oxo, C_{1-6} alkyl, or halogen, wherein the C_{1-6} alkyl is optionally substituted with one or more halogen.

15. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is selected from the group consisting of , , , , , , , and .

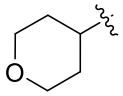
16. The compound of any one of claims 1-15, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein

(a) R^3 is C_{6-14} aryl, which is independently optionally substituted with one or more R^{31}; optionally wherein R^3 is phenyl, which is optionally substituted with one or more R^{31};

(b) R^3 is 5- to 12-membered heteroaryl, which is independently optionally substituted with one or more R^{31}; optionally wherein R^3 is selected from the group consisting of:



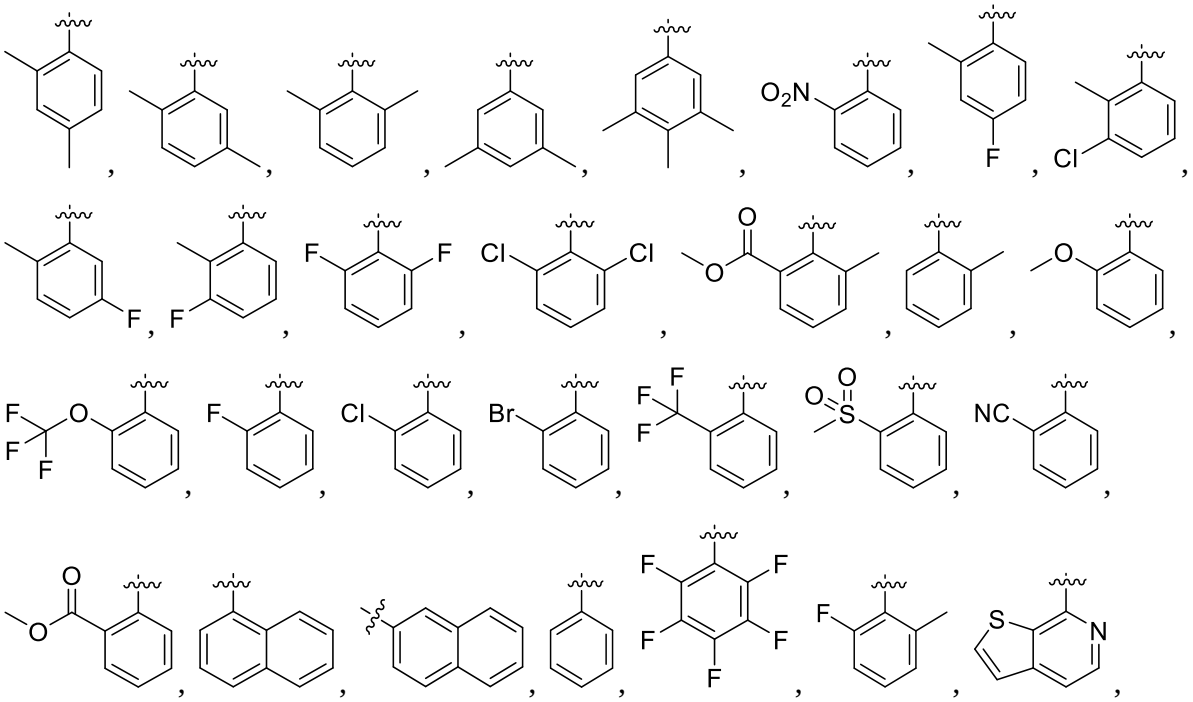
, each of which is independently optionally substituted with one or more R^{31}; or

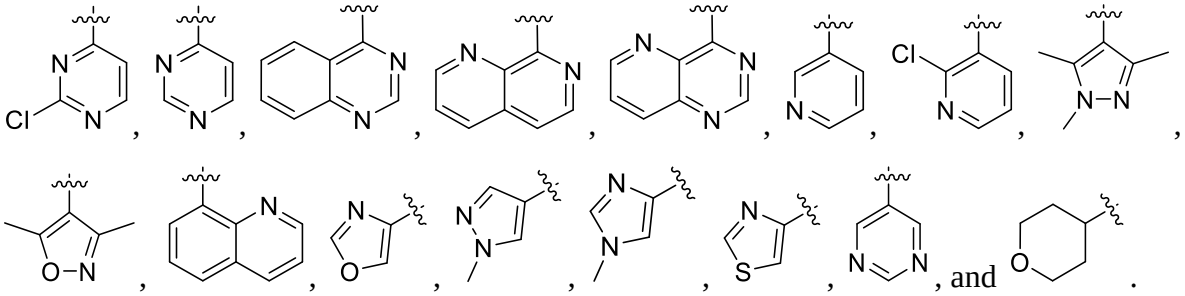
(c) R^3 is 3- to 12- membered heterocyclyl, which is independently optionally substituted with one or more R^{31}; optionally wherein R^3 is 

, which is independently optionally substituted with one or more R^{31}.

17. The compound of any one of claims 1-16, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{31} is independently C_{1-6} alkyl, -CN, $-NO_2$, halogen, $-OR^{3a}$, $-C(O)OR^{3a}$, or $-S(O)_2R^{3a}$, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and –CN.

18. The compound of any one of claims 1-15, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is selected from the group consisting of:

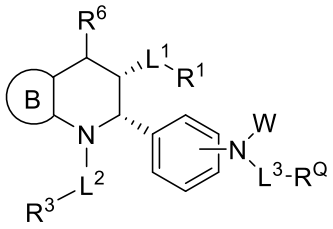




19. The compound of any one of claims 1-18, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is *-C(O)NH-**.

20. The compound of any one of claims 1-19, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is –C(O)-.

21. The compound of claim 1, where the compound is of formula (VIII),



(VIII).

22. A compound selected from the group consisting of the compounds in Table 1, or a pharmaceutically acceptable salt of any of the foregoing.

23. A pharmaceutical composition comprising the compound of any one of claims 1-22, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.

24. Use of a compound of any one of claims 1-22, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for inhibiting C5a receptor.

25. Use of a compound of any one of claims 1-22, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating a disorder mediated by the complement pathways; optionally

wherein the disorder is an inflammatory disease, a cardiovascular or cerebrovascular disease, or an autoimmune disease or wherein the disease or disorder is at least selected from the group consisting of: macular degeneration (MD), age-related macular degeneration (AMD), ischemia reperfusion injury, arthritis, rheumatoid arthritis, lupus, ulcerative colitis, stroke, post-surgery systemic inflammatory syndrome, asthma, allergic asthma, chronic obstructive

pulmonary disease (COPD), paroxysmal nocturnal hemoglobinuria (PNH) syndrome, autoimmune hemolytic anemia (AIHA), Gaucher disease, myasthenia gravis, neuromyelitis optica, (NMO), multiple sclerosis, delayed graft function, antibody-mediated rejection, atypical hemolytic uremic syndrome (aHUS), central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), epidermolysis bullosa, sepsis, septic shock, organ transplantation, inflammation (including, but not limited to, inflammation associated with cardiopulmonary bypass surgery and kidney dialysis), C3 glomerulopathy, membranous nephropathy, IgA nephropathy, glomerulonephritis (including, but not limited to, anti-neutrophil cytoplasmic antibody (ANCA)-mediated glomerulonephritis, lupus nephritis, and combinations thereof), ANCA-mediated vasculitis, Shiga toxin induced HUS, and antiphospholipid antibody-induced pregnancy loss, graft versus host disease (GVHD), bullous pemphigoid, hidradenitis suppurativa, dermatitis herpetiformis, sweets syndrome, pyoderma gangrenosum, palmo-plantar pustulosis & pustular psoriasis, rheumatoid neutrophilic dermatoses, subcorneal pustular dermatosis, bowel-associated dermatosis-arthritis syndrome, neutrophilic eccrine hidradenitis, linear IgA disease, or any combinations thereof.

26. A compound of any one of claims 1-22, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, for use in therapy.