HPD INHIBITOR COMPOSITIONS AND METHODS OF USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Greek Patent Application No. 20240100223 filed March 27, 2024, the content of which is incorporated herein by reference in its entirety for all purposes.

FIELD OF DISCLOSURE

[0002] The present disclosure relates to compounds for modulating or inhibiting 4-hydroxyphenylpyruvate dioxygenase (HPD) that have decreased inhibitory activity against sepiapterin reductase (SPR), their use in therapeutic methods of treating conditions and disorders, and their use in method for controlling weeds.

BACKGROUND

[0003] Tyrosinemia type I can be characterized by the lack of activity of the enzyme fumarylacetoacetate hydrolase (FAH), resulting in impaired tyrosine metabolism and the accumulation of tyrosine and metabolic byproducts. The 4-hydroxyphenylpyruvate dioxygenase (commonly abbreviated to HPD or HPPD) inhibitor nitisinone is the standard-of-care for the inborn error of tyrosinemia type I. It has been reported that subjects with tyrosinemia type I develop progressive neurocognitive decline, the causation of which is unknown, but which may be attributable to treatment with nitisinone. Thus, there is a need for compounds and methods of treatment for modulating or inhibiting HPD that do not contribute to neurocognitive decline.

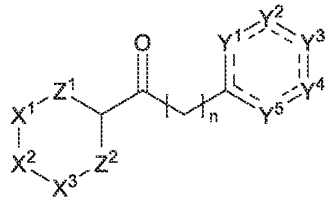
[0004] In addition, various HPD inhibitors have herbicidal properties. Considering these triketone herbicides are routinely used on commercial crops for human consumption and enter the human food chain, there is a need for compounds, herbicidal compositions, and methods of treating weeds associated with modulating or inhibiting HPD activity that do not have off-target effects which may be toxic to humans and other mammals.

SUMMARY

[0005] The present disclosure provides compounds that inhibit HPD with no or minimal inhibition of SPR. The present disclosure also provides methods of treatment, methods of using

compounds, pharmaceutical formulations, and medicaments for treating inborn errors of metabolism (*e.g.*, conditions responsive to modulation or inhibition of HPD, such as tyrosinemia) in a subject in need thereof by inhibition of HPD with no or minimal inhibition of SPR.

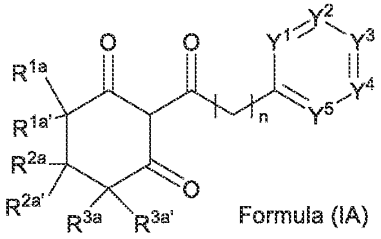
[0006] The present disclosure provides a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all === together form an aryl ring or heteroaryl ring, wherein X^1, X^2, X^3, Z^1, Z^2, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described herein.

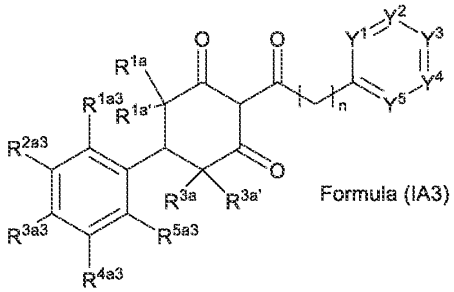
[0007] In some embodiments, the compound of Formula (I) is a compound of Formula (IA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IA)

wherein R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, $R^{3a'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

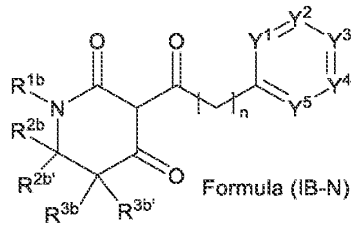
[0008] In some embodiments, the compound of Formula (IA) is a compound of Formula (IA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IA3)

wherein R^{1a}, $R^{1a'}$, R^{3a}, $R^{3a'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

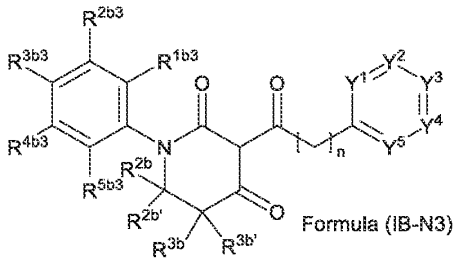
[0009] In some embodiments, the compound of Formula (I) is a compound of Formula (IB-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IB-N)

wherein R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, $R^{3b'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

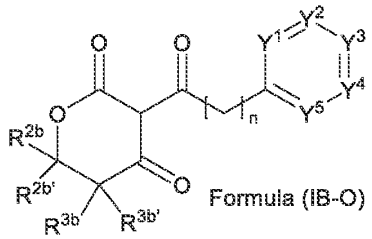
[0010] In some embodiments, the compound of Formula (IB-N) is a compound of Formula (IB-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IB-N3)

wherein R^{2b}, $R^{2b'}$, R^{3b}, $R^{3b'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

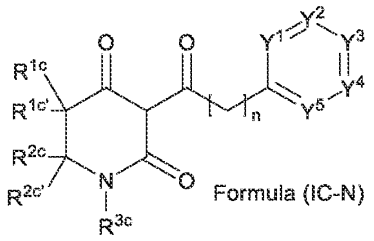
[0011] In some embodiments, the compound of Formula (I) is a compound of Formula (IB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IB-O)

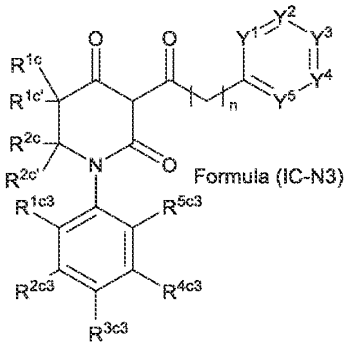
wherein R^{2b}, $R^{2b'}$, R^{3b}, $R^{3b'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

[0012] In some embodiments, the compound of Formula (I) is a compound of Formula (IC-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



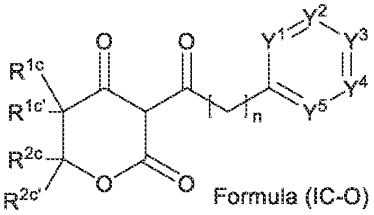
wherein R^{1c}, $R^{1c'}$, R^{2c}, $R^{2c'}$, R^{3c}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

[0013] In some embodiments, the compound of Formula (IC-N) is a compound of Formula (IC-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



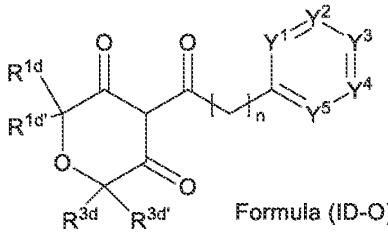
wherein R^{1c}, $R^{1c'}$, R^{2c}, $R^{2c'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

[0014] In some embodiments, the compound of Formula (I) is a compound of Formula (IC-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



wherein R^{1c}, $R^{1c'}$, R^{2c}, $R^{2c'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

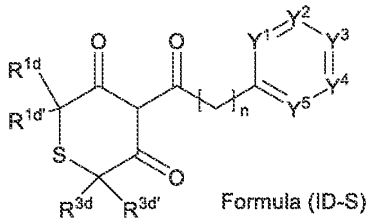
[0015] In some embodiments, the compound of Formula (I) is a compound of Formula (ID-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (ID-O)

wherein R^{1d}, $R^{1d'}$, R^{3d}, $R^{3d'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

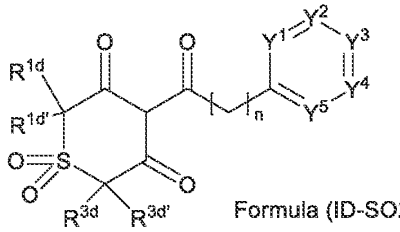
[0016] In some embodiments, the compound of Formula (I) is a compound of Formula (ID-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (ID-S)

wherein R^{1d}, $R^{1d'}$, R^{3d}, $R^{3d'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

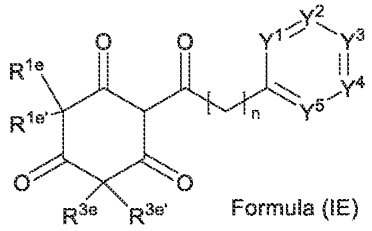
[0017] In some embodiments, the compound of Formula (I) is a compound of Formula (ID-SO2), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (ID-SO2)

wherein R^{1d}, $R^{1d'}$, R^{3d}, $R^{3d'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

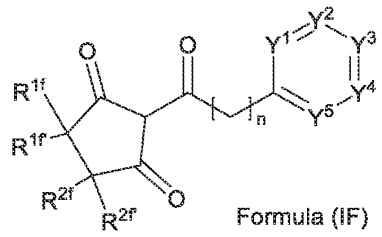
[0018] In some embodiments, the compound of Formula (I) is a compound of Formula (IE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IE)

wherein R^{1e}, $R^{1e'}$, R^{3e}, $R^{3e'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

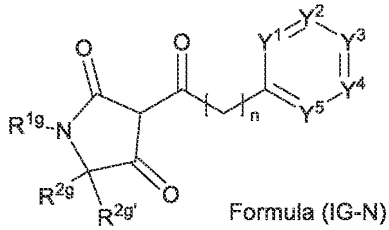
[0019] In some embodiments, the compound of Formula (I) is a compound of Formula (IF), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IF)

wherein R^{1f}, $R^{1f'}$, R^{2f}, $R^{2f'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

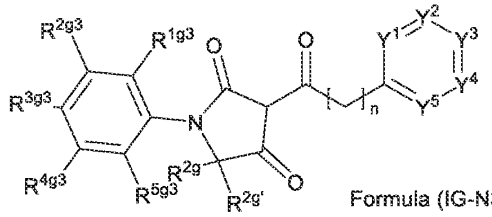
[0020] In some embodiments, the compound of Formula (I) is a compound of Formula (IG-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG-N)

wherein R^{1g}, R^{2g}, $R^{2g'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

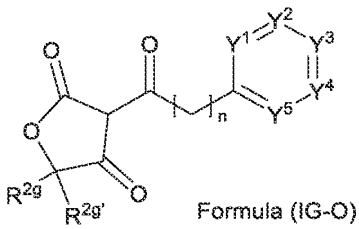
[0021] In some embodiments, the compound of Formula (IG-N) is a compound of Formula (IG-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG-N3)

wherein R^{2g}, $R^{2g'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

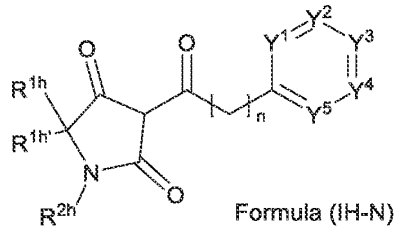
[0022] In some embodiments, the compound of Formula (I) is a compound of Formula (IG-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG-O)

wherein R^{2g}, $R^{2g'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

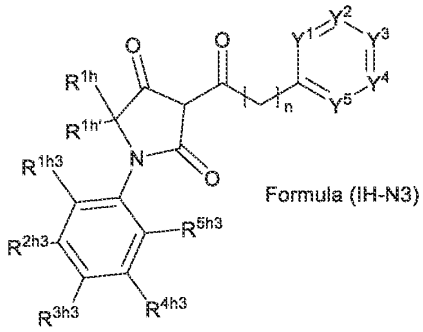
[0023] In some embodiments, the compound of Formula (I) is a compound of Formula (IH-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-N)

wherein R^{1h}, $R^{1h'}$, R^{2h}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

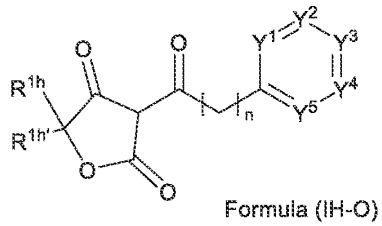
[0024] In some embodiments, the compound of Formula (IH-N) is a compound of Formula (IH-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-N3)

wherein R^{1h}, $R^{1h'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

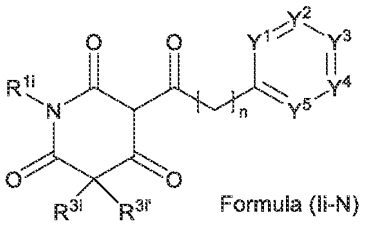
[0025] In some embodiments, the compound of Formula (I) is a compound of Formula (IH-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-O)

wherein R^{1h}, $R^{1h'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

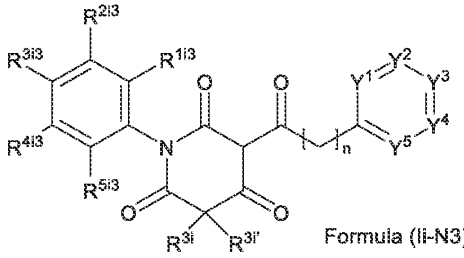
[0026] In some embodiments, the compound of Formula (I) is a compound of Formula (Ii-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (Ii-N)

wherein R^{1i}, R^{3i}, $R^{3i'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

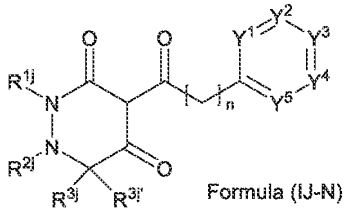
[0027] In some embodiments, the compound of Formula (Ii-N) is a compound of Formula (Ii-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (Ii-N3)

wherein R^{3i}, $R^{3i'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1i3}, R^{2i3}, R^{3i3}, R^{4i3}, and R^{5i3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

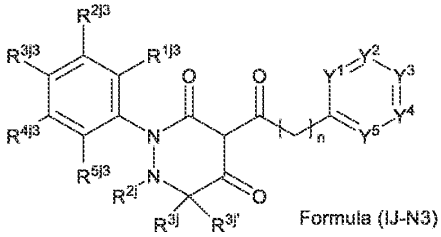
[0028] In some embodiments, the compound of Formula (I) is a compound of Formula (IJ-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IJ-N)

wherein R^{1j}, R^{2j}, R^{3j}, $R^{3j'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

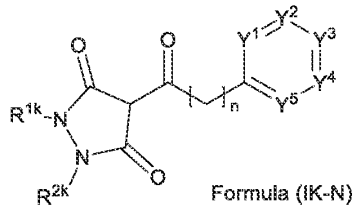
[0029] In some embodiments, the compound of Formula (IJ-N) is a compound of Formula (IJ-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IJ-N3)

wherein R^{2j}, R^{3j}, $R^{3j'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1j3}, R^{2j3}, R^{3j3}, R^{4j3}, and R^{5j3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

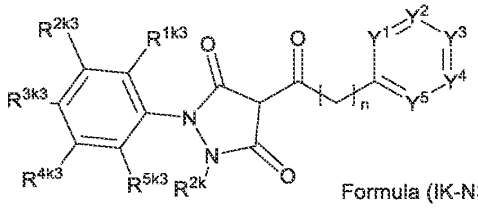
[0030] In some embodiments, the compound of Formula (I) is a compound of Formula (IK-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IK-N)

wherein R^{1k}, R^{2k}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

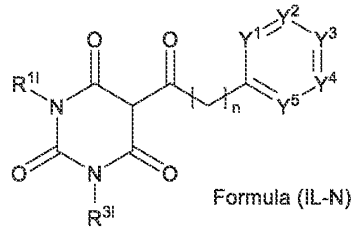
[0031] In some embodiments, the compound of Formula (IK-N) is a compound of Formula (IK-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IK-N3)

wherein R^{2k}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1k3}, R^{2k3}, R^{3k3}, R^{4k3}, and R^{5k3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

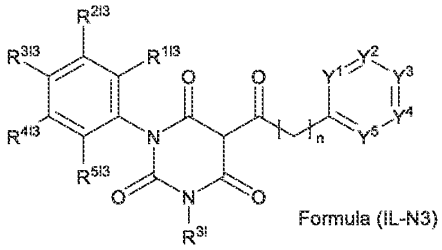
[0032] In some embodiments, the compound of Formula (I) is a compound of Formula (IL-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IL-N)

wherein R^{1l}, R^{3l}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

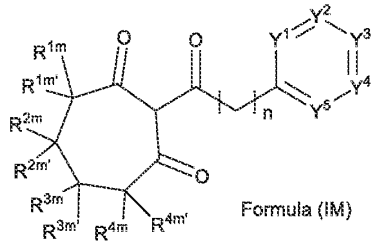
[0033] In some embodiments, the compound of Formula (IL-N) is a compound of Formula (IL-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IL-N3)

wherein R^{3l}, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I), and R^{1l3}, R^{2l3}, R^{3l3}, R^{4l3}, and R^{5l3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

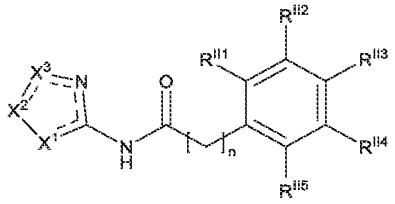
[0034] In some embodiments, the compound of Formula (I) is a compound of Formula (IM), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IM)

wherein R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, $R^{4m'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (I).

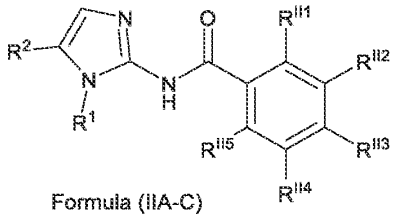
[0035] The present disclosure also provides a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein X^1, X^2, X^3, n, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described herein.

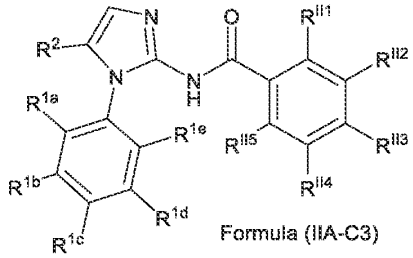
[0036] In some embodiments, the compound of Formula (II) is a compound of Formula (IIA-C), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-C)

wherein R^1, R^2, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II).

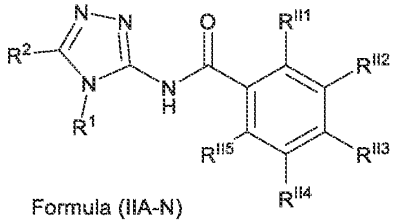
[0037] In some embodiments, the compound of Formula (IIA-C) is a compound of Formula (IIA-C3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-C3)

wherein R^2, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II), and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

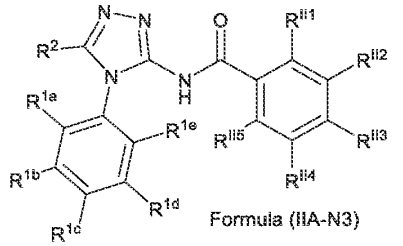
[0038] In some embodiments, the compound of Formula (II) is a compound of Formula (IIA-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N)

wherein R^1, R^2, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II).

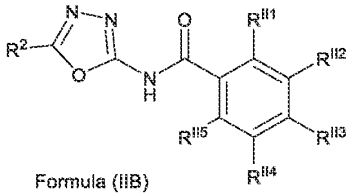
[0039] In some embodiments, the compound of Formula (IIA-N) is a compound of Formula (IIA-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N3)

wherein R^2, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II), and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

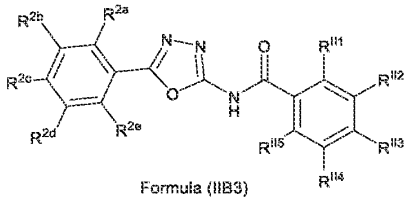
[0040] In some embodiments, the compound of Formula (II) is a compound of Formula (IIB), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIB)

wherein R^2, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II).

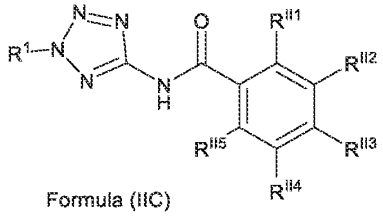
[0041] In some embodiments, the compound of Formula (IIB) is a compound of Formula (IIB3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIB3)

wherein R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II), and R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

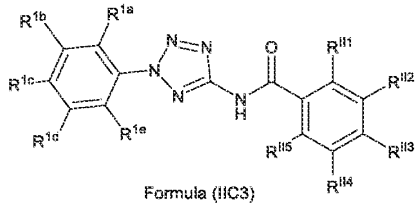
[0042] In some embodiments, the compound of Formula (II) is a compound of Formula (IIC), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIC)

wherein R^1, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II).

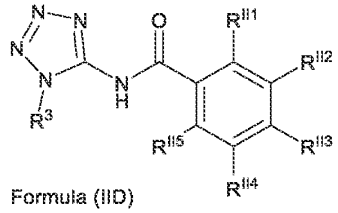
[0043] In some embodiments, the compound of Formula (IIC) is a compound of Formula (IIC3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIC3)

wherein R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II), and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

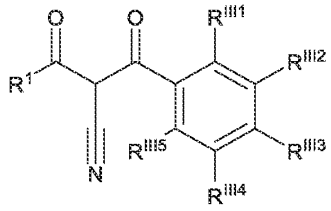
[0044] In some embodiments, the compound of Formula (II) is a compound of Formula (IID), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IID)

wherein R^3, R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are as described for Formula (II).

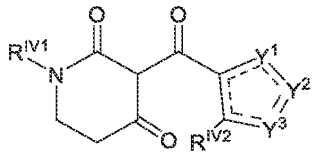
[0045] The present disclosure also provides a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1, R^{III1}, R^{III2}, R^{III3}, R^{III4}, and R^{III5} are as described herein.

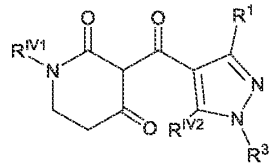
[0046] The present disclosure also provides a compound of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein Y^1, Y^2, Y^3, R^{IV1}, and R^{IV2} are as described herein.

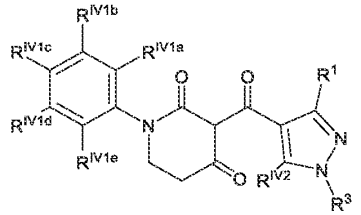
[0047] In some embodiments, the compound of Formula (IV) is a compound of Formula (IVA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVA)

wherein R^1, R^3, R^{IV1}, and R^{IV2} are as described for Formula (IV).

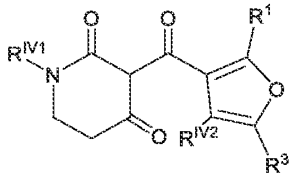
[0048] In some embodiments, the compound of Formula (IVA) is a compound of Formula (IVA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVA3)

wherein R^1, R^3, and R^{IV2} are as described for Formula (IV), and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

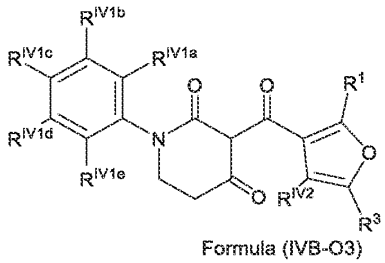
[0049] In some embodiments, the compound of Formula (IV) is a compound of Formula (IVB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O)

wherein R^1, R^3, R^{IV1}, and R^{IV2} are as described for Formula (IV).

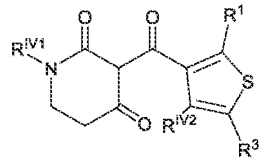
[0050] In some embodiments, the compound of Formula (IVB-O) is a compound of Formula (IVB-O3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O3)

wherein R^1, R^3, and R^{IV2} are as described for Formula (IV), and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

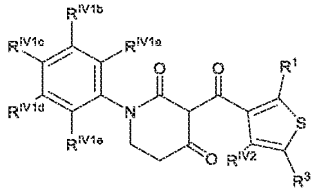
[0051] In some embodiments, the compound of Formula (IV) is a compound of Formula (IVB-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S)

wherein R^1, R^3, R^{IV1}, and R^{IV2} are as described for Formula (IV).

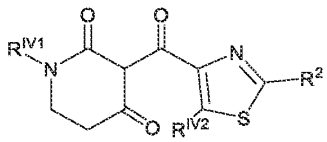
[0052] In some embodiments, the compound of Formula (IVB-S) is a compound of Formula (IVB-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S3)

wherein R^1, R^3, and R^{IV2} are as described for Formula (IV), and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

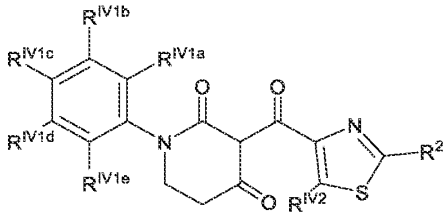
[0053] In some embodiments, the compound of Formula (IV) is a compound of Formula (IVC-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S)

wherein R^2, R^{IV1}, and R^{IV2} are as described for Formula (IV).

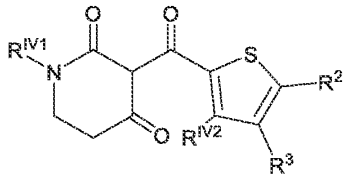
[0054] In some embodiments, the compound of Formula (IVC-S) is a compound of Formula (IVC-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S3)

wherein R^2 and R^{IV2} are as described for Formula (IV), and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

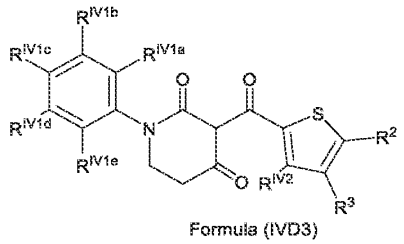
[0055] In some embodiments, the compound of Formula (IV) is a compound of Formula (IVD), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD)

wherein R^2, R^3, R^{IV1}, and R^{IV2} are as described for Formula (IV).

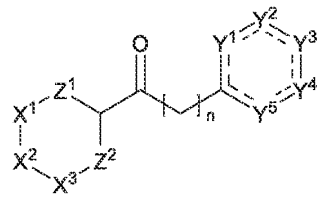
[0056] In some embodiments, the compound of Formula (IVD) is a compound of Formula (IVD3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD3)

wherein R^2, R^3, and R^{IV2} are as described for Formula (IV), and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

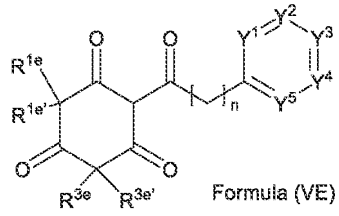
[0057] The present disclosure also provides methods of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all ≡ together form an aryl ring or heteroaryl ring, wherein X^1, X^2, X^3, Z^1, Z^2, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described herein.

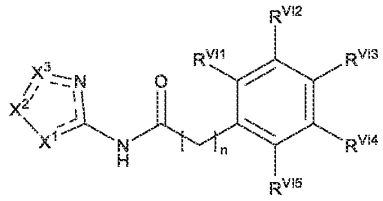
[0058] In some embodiments, the compound of Formula (V) is a compound of Formula (VE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (VE)

wherein R^{1e}, $R^{1e'}$, R^{3e}, $R^{3e'}$, n, Y^1, Y^2, Y^3, Y^4, and Y^5 are as described for Formula (II).

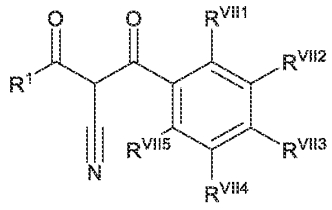
[0059] The present disclosure also provides methods of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI):



Formula (VI)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein X^1, X^2, X^3, n, R^{VI1}, R^{VI2}, R^{VI3}, R^{VI4}, and R^{VI5} are as described herein.

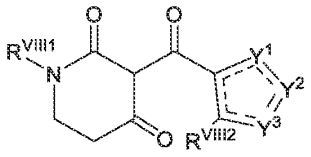
[0060] The present disclosure also provides methods of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1, R^{VII1}, R^{VII2}, R^{VII3}, R^{VII4}, and R^{VII5} are as described herein.

[0061] The present disclosure also provides methods of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII):



Formula (VIII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein Y^1, Y^2, Y^3, R^{VIII1}, and R^{VIII2} are as described herein.

[0062] The present disclosure also provides methods of treating a condition in a subject in need thereof (*e.g.*, a condition that is responsive to modulation or inhibition of HPD), the method comprising administering a therapeutically effective amount of a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0063] The present disclosure also provides for use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising: administering to the subject an effective amount of the compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE),

(IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0064] The present disclosure also provides for use of a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising: administering to the subject an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0065] The present disclosure also provides for use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and the compound is of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0066] The present disclosure also provides for use of a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt,

stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0067] The present disclosure also provides for a compound for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising: administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject, wherein the compound is of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0068] The present disclosure also provides for the compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising: administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject.

[0069] The present disclosure also provides for a pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein: the method comprises administering the pharmaceutical formulation to a subject having the condition, and the compound is of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-

C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0070] The present disclosure also provides for a pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein: the method comprises administering the pharmaceutical formulation to a subject having the condition.

[0071] The present disclosure also provides for a medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein: the treatment comprises administering the medicament to a subject having the condition, and the compound is of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0072] The present disclosure also provides for a medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of the compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a

pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein: the treatment comprises administering the medicament to a subject having the condition.

[0073] The present disclosure also provides for an herbicidal composition comprising the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or an agriculturally acceptable salt thereof.

[0074] The present disclosure also provides for a method of controlling a weed, comprising administering the herbicidal composition comprising the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or an agriculturally acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0075] **FIG. 1** shows the growth of DLD1 cells expressing phenylalanine hydroxylase (PAH) and lacking PAH in tyrosine-free and complete media treated with nitisinone and other triketones.

[0076] **FIG. 2** shows the effect of nitisinone on PAH-dependent tyrosine synthesis in DLD1-EV or DLD1-PAH cells were cultured in media with uniformly ^{13}C-labelled phenylalanine (m+9).

[0077] **FIG. 3** shows the effect of nitisinone treatment on A549-PAH cells in the presence and absence of tyrosine with tetrahydrobiopterin (BH4) supplementation.

[0078] **FIG. 4** shows the effect of nitisinone on DLD1-PAH cells in tyrosine-free media in the presence and absence of BH4 or dihydrobiopterin (BH2).

[0079] **FIG. 5** shows the effect of nitisinone on BH4 - and BH2 levels in DLD1-EV and DLD1-PAH cells.

[0080] **FIG. 6** shows the effect of nitisinone on BH2 levels in Kelly and SKNBE(2) cells.

[0081] **FIG. 7** shows the effect of nitisinone on biopterin levels in DLD1-EV/PAH, Kelly and SKNBE(2) cells.

[0082] **FIG. 8** shows the effect of nitisinone on sepiapterin levels in DLD1-EV/PAH, Kelly and SKNBE(2) cells.

[0083] **FIG. 9A-9L** show *in vitro* activity of SPR and the effects of SPR inhibitors and triketones on SPR activity.

[0084] **FIG. 10** shows the effect of nitisinone and other HPD-targeting inhibitors on recombinant mouse SPR.

[0085] **FIG. 11** shows the effect of nitisinone on plasma and brain sepiapterin levels in wild-type Balb/c mice.

[0086] **FIG. 12** shows the effect of nitisinone on the ability of mice to learn, as assessed via a Morris Water Maze.

[0087] **FIG. 13** shows the effect of nitisinone on the behavior of mice in an open field test.

DETAILED DESCRIPTION

[0088] The following description sets forth numerous exemplary compounds, methods, uses, and the like. 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.

[0089] As used herein, the terms "including," "containing," and "comprising" are used in their open, non-limiting sense.

[0090] The articles "a" and "an," as used herein, refer to one or more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" refers to one element or more than one element.

[0091] To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about." It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular

stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

Inborn Errors of Metabolism

[0092] Inborn errors of metabolism are a heterologous group of disorders characterized by the failure of metabolic pathways involved in metabolism of nutrients, including, but not limited to: carbohydrates, fatty acids, proteins, and amino acids. Inborn errors of metabolism arise from congenital defects in enzymatic or transport protein activity resulting in metabolic deviations that can comprise accumulation of toxic substrates or defects in energy production. Inborn errors of metabolism usually present in the neonatal period or infancy, but can present even in adulthood.

[0093] In humans, tyrosine is synthesized from the essential amino acid phenylalanine. Tyrosine or phenylalanine may be derived from food or derived from drugs, *e.g.*, parenteral nutrition products. The conversion of phenylalanine to tyrosine is catalyzed by the enzyme phenylalanine hydroxylase (PAH), a monooxygenase. As a proteinogenic amino acid, tyrosine is required for protein synthesis. Furthermore, tyrosine is a key constituent of proteins that are part of signal transduction processes and functions as a receiver of phosphate groups that are transferred by way of protein kinases.

Tyrosine bioavailability is governed by multiple factors, including dietary availability of tyrosine and phenylalanine, the uptake and transport of these amino acids from the GI tract, the biosynthesis of tyrosine from phenylalanine (via PAH), protein breakdown and recycling (*e.g.*, via autophagy) and the rate of tyrosine utilization in anabolic pathways such as protein synthesis. Within cells, tyrosine metabolism is carefully regulated through the activities of multiple enzymes. Tyrosine is synthesized from the amino acid phenylalanine through the activity of phenylalanine hydroxylase (PAH), requiring tetrahydrobiopterin (BH4) as a cofactor. Additional enzymes in the tyrosine metabolism included tyrosine aminotransferase (TAT), 4-hydroxyphenylpyruvate dioxygenase (HPD), homogentisate 1,2-dioxygenase (HGD), glutathione S-transferase zeta 1 (GSTZ1), and fumarylacetoacetate hydrolase (FAH). The concerted activity of these enzymes results in the production of fumarate that is utilized by cells as a substrate for energy production.

[0094] Sepiapterin reductase (SPR) is an enzyme involved in BH4 de novo biosynthesis and BH4 salvaging, ensuring that cells have adequate levels of BH4 necessary for cellular functions,

including tyrosine synthesis. In BH4 de novo biosynthesis, SPR catalyzes the NADPH-dependent reduction of 6-pyruvolytetrahydropterin to BH4. Furthermore, in BH4 salvaging, following uptake of sepiapterin, SPR catalyzes the NAPDH-dependent reduction of sepiapterin into 7,8-BH2, which can then be utilized as a source for BH4.

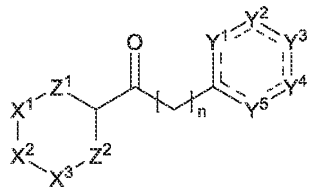
[0095] At any point in the tyrosine metabolic pathway, deficits in enzymatic activity can result in metabolic defects. Multiple inborn errors of metabolism are a result of these deficits. Phenylketonuria results from loss of PAH function, tyrosinemia type II results from loss of TAT function, tyrosinemia type III results from loss of HPD function, alkaptonuria results from loss of HGD function, and tyrosinemia type I results from loss of FAH activity.

[0096] Tyrosinemia type I occurs in individuals lacking FAH function and presents in either acute or chronic form. Acute tyrosinemia type I presents at birth or during the first months of life with individuals presenting with failure to gain weight and a failure to thrive that can later progress to developmental delays, liver failure, and blood-clotting abnormalities that can lead to death. Prior to the discovery of the small molecule HPD inhibitor nitisinone, tyrosinemia type I was fatal in childhood without a liver transplant. Nitisinone is the standard of care for tyrosinemia type I and is effective at managing the disease across the life of an individual. However, chronic administration of nitisinone is associated with neurocognitive decline in individuals due to a hereto unknown mechanism. Applicant has made the surprising discovery that nitisinone can inhibit SPR, which can result in BH4 cofactor deficiency, which in turn can result in neurocognitive decline, an unintended effect of nitisinone and other HPD inhibitors. Embodiments of the present disclosure are directed to practical applications of that surprising result (*e.g.*, SPR-sparing HPD inhibitors, and methods of treating conditions and disorders associated responsive to modulation or inhibition of HPD with SPR-sparing HPD inhibitors.)

SPR-sparing HPD specific inhibitors

[0097] In some embodiments, the disclosure provides compositions comprising compounds that inhibit HPD, but have no or minimal inhibitory activity for SPR, and methods of using such compositions, thereby reducing or eliminating side effects in subjects caused by currently available standard-of-care for treating inborn errors of metabolism.

[0098] In some embodiments, the disclosure provides a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all ═══ together form an aryl ring or heteroaryl ring, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond;

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$;

X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$;

X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond;

X^1 is NR^{1l} or O, X^2 is C(O), and X^3 is NR^{3l} or O; or

X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$;

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl; wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3i} and $R^{3i'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3i} or $R^{3i'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3j} and $R^{3j'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3j} or $R^{3j'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{2h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1i} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1i} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1j} and R^{2j} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1j} or R^{2j} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1k} and R^{2k} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1k} or R^{2k} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, or CN;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic

ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$, then:

Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; or

Y^1 is C(O); Y^2 is $N(R^{2b2'})$; Y^3 is $C(R^{3b2'})$; Y^4 is $C(R^{4b2'})$; and Y^5 is N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN;

$R^{2b2'}$ is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

$R^{3b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

$R^{4b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

$R^{2b2'}$ combines with $R^{3b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{4b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{4b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

$R^{3b2'}$ combines with $R^{4b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{2b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4c2} combines with R^{5c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{3c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} is Cl; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl, NO_2, or SO_2-C_{1-6} alkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} is NO_2; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic

ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$; then Y^1 is $C(R^{1i2})$ or N; Y^2 is $C(R^{2i2})$ or N; Y^3 is $C(R^{3i2})$ or N; Y^4 is $C(R^{4i2})$ or N; and Y^5 is $C(R^{5i2})$ or N; wherein

R^{1i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1i2} combines with R^{2i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2i2} combines with R^{3i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3i2} combines with R^{4i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4i2} combines with R^{5i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{3i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$; then Y^1 is $C(R^{1j2})$ or N; Y^2 is $C(R^{2j2})$ or N; Y^3 is $C(R^{3j2})$ or N; Y^4 is $C(R^{4j2})$ or N; and Y^5 is $C(R^{5j2})$ or N; wherein

R^{1j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1j2} combines with R^{2j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2j2} combines with R^{3j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3j2} combines with R^{4j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4j2} combines with R^{5j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{3j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond; then Y^1 is $C(R^{1k2})$ or N; Y^2 is $C(R^{2k2})$ or N; Y^3 is $C(R^{3k2})$ or N; Y^4 is $C(R^{4k2})$ or N; and Y^5 is $C(R^{5k2})$ or N; wherein

R^{1k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1k2} combines with R^{2k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2k2} combines with R^{3k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3k2} combines with R^{4k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4k2} combines with R^{5k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{3k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1l} or O, X^2 is C(O), and X^3 is NR^{3l} or O; then Y^1 is $C(R^{112})$ or N; Y^2 is $C(R^{212})$ or N; Y^3 is $C(R^{312})$ or N; Y^4 is $C(R^{412})$ or N; and Y^5 is $C(R^{512})$ or N; wherein

R^{112} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{212} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{312} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{412} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{512} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{112} combines with R^{212} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{312}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{212} combines with R^{312} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{312} combines with R^{412} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{412} combines with R^{512} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{312} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

or

if X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$; then Y^1 is $C(R^{1m2})$ or N; Y^2 is $C(R^{2m2})$ or N; Y^3 is $C(R^{3m2})$ or N; Y^4 is $C(R^{4m2})$ or N; and Y^5 is $C(R^{5m2})$ or N; wherein

R^{1m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1m2} combines with R^{2m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2m2} combines with R^{3m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3m2} combines with R^{4m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4m2} combines with R^{5m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{3m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN.

[0099] In some embodiments of the compounds of Formula (I):

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; or

X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l};

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^{1a} and $R^{1a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ are each H; orR^{2a} and $R^{2a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H; or

R^{1a} and R^{3a} combine to form a cycloalkyl ring, wherein the cycloalkyl ring may be unsubstituted or substituted with one or more C_{1-6} alkyl, and $R^{1a'}$, R^{2a}, $R^{2a'}$, and $R^{3a'}$ are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3b} and $R^{3b'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$;

wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{3e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{4e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{5e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2; or

R^{1e2} combines with R^{2e2} to form a heteroaryl ring, and R^{3e2}, R^{4e2}, and R^{5e2} are each H;

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l}; then Y^1 is $C(R^{1l2})$; Y^2 is $C(R^{2l2})$; Y^3 is $C(R^{3l2})$; Y^4 is $C(R^{4l2})$; and Y^5 is $C(R^{5l2})$; wherein

R^{1l2} is H, C_{1-6} haloalkyl, or NO_2;

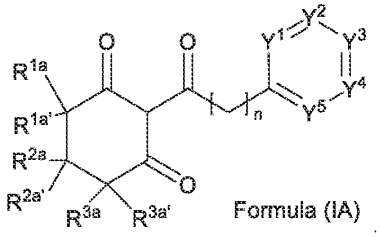
R^{2l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5l2} is H, C_{1-6} haloalkyl, or NO_2.

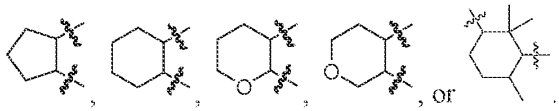
[0100] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



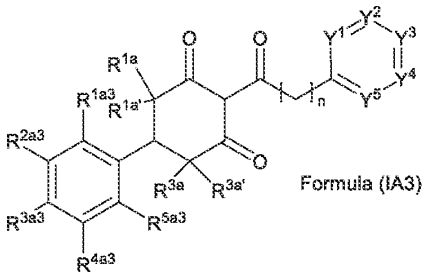
Formula (IA)

[0101] In some embodiments of the compounds of Formulae (I) and (IA), or the pharmaceutically acceptable salts or tautomers thereof, R^{3a} and $R^{3a'}$ are each C_{1-6} alkyl. In some embodiments, R^{3a} and $R^{3a'}$ are each C_{1-6} alkyl, and R^{1a}, $R^{1a'}$, R^{2a}, and $R^{2a'}$ are each H. In some embodiments, R^{2a} and $R^{2a'}$ are C_{3-6} cycloalkyl and H respectively. In some embodiments, R^{2a} and $R^{2a'}$ are C_{3-6} cycloalkyl and H respectively, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H. In some embodiments, R^{1a} and $R^{1a'}$ are -CO(O)-C_{1-6} alkyl and H respectively. In some embodiments, R^{1a} and $R^{1a'}$ are -CO(O)-C_{1-6} alkyl and H respectively, and R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ are each H. In

some embodiments, R^{2a} and $R^{2a'}$ are -CO(O)-C_{1-6} alkyl and H respectively. In some embodiments, R^{2a} and $R^{2a'}$ are -CO(O)-C_{1-6} alkyl and H respectively, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H. In some embodiments, two or more of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl. In some embodiments, R^{1a} and $R^{1a'}$, R^{2a} and $R^{2a'}$, or R^{3a} and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring. In some embodiments, R^{1a} and R^{2a}, R^{2a} and R^{3a}, or R^{1a} and R^{3a} combine to form a cycloalkyl ring or heterocyclic ring.

[0102] In some embodiments, R^{1a} and R^{2a}, R^{2a} and R^{3a}, or R^{1a} and R^{3a} combine to form a C_{1-6} cycloalkyl ring. In some embodiments, R^{1a} and R^{2a}, R^{2a} and R^{3a}, or R^{1a} and R^{3a} combine to form a C_{1-8} cycloalkyl ring. In some embodiments, R^{1a} and R^{2a}, R^{2a} and R^{3a}, or R^{1a} and R^{3a} combine to form a heterocyclic ring comprising 4 to 8 atoms carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, R^{1a} and R^{2a}, R^{2a} and R^{3a}, or R^{1a} and R^{3a} combine to form .

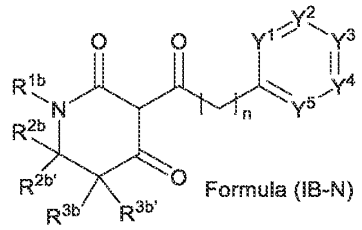
[0103] In some embodiments, the compound of Formula (IA), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



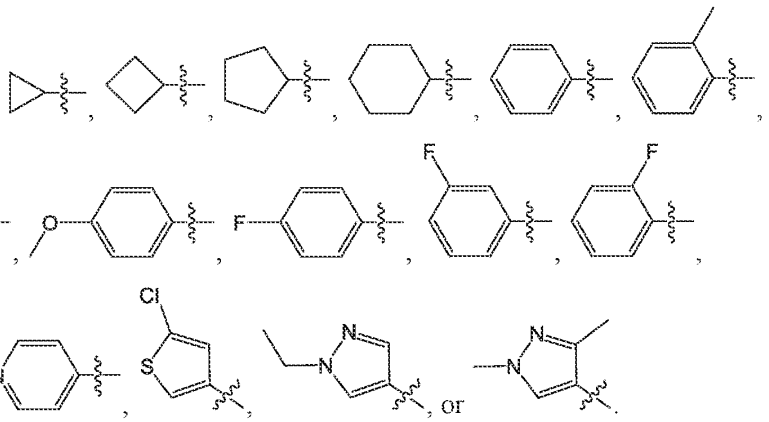
Formula (IA3)

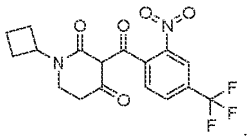
[0104] In some embodiments, the compound of Formula (I) or (IA) is a compound of Formula (IA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each H. In some embodiments, R^{4a3} is -O-C_{1-6} alkyl. In some embodiments, R^{4a3} is -O-C_{1-6} alkyl, and R^{1a3}, R^{2a3}, R^{3a3}, and R^{5a3} are each H.

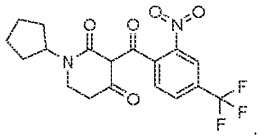
[0105] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IB-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

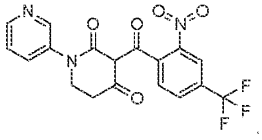


Formula (IB-N)

[0106] In some embodiments of the compounds of Formulae (I) and (IB-N), or the pharmaceutically acceptable salts or tautomers thereof, R^{1b} is cycloalkyl, aryl, or heteroaryl. In some embodiments, R^{1b} is 

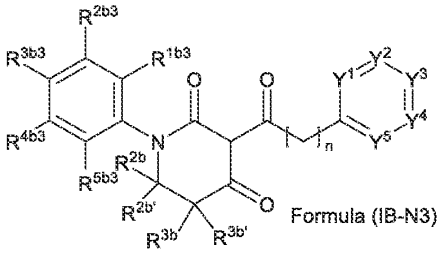
[0107] In some embodiments, the compound of Formula (IB-N) is 

. In some embodiments, the compound of Formula (IB-N) is 

. In some embodiments, the compound of Formula (IB-N) is 

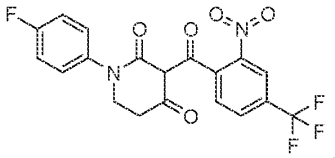
.

[0108] In some embodiments, the compound of Formula (IB-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IB-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

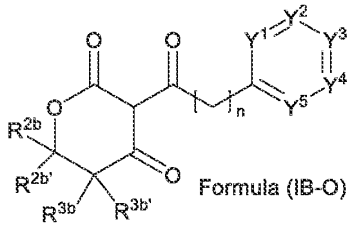


[0109] In some embodiments, the compound of Formula (I) or (IB-N) is a compound of Formula (IB-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, one of R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, or R^{5b3} is F, and the others are each H. In some embodiments, R^{3b3} is F, and R^{1b3}, R^{2b3}, R^{4b3}, and R^{5b3} are each H. In some embodiments, R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each H.

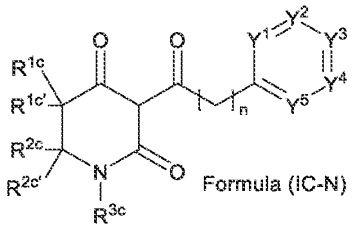
[0110] In some embodiments, the compound of Formula (IB-N3) is



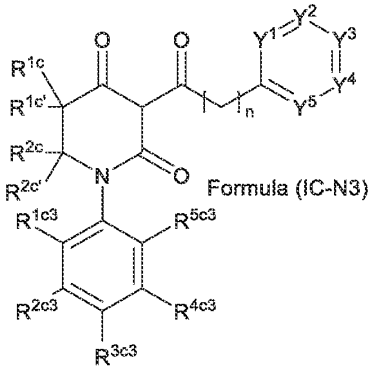
[0111] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



[0112] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IC-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

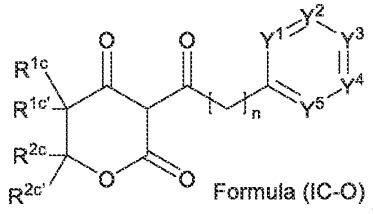


[0113] In some embodiments, the compound of Formula (IC-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IC-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

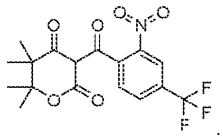


[0114] In some embodiments, the compound of Formula (I) or (IC-N) is a compound of Formula (IC-N3), or s pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each H.

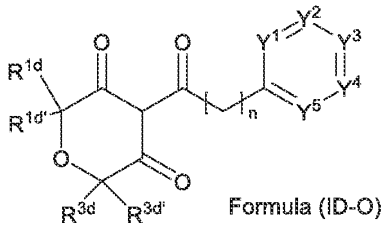
[0115] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IC-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



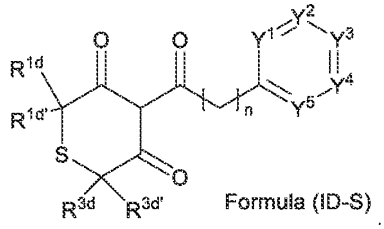
[0116] In some embodiments of the compounds of Formulae (I) and (IC-O), or the pharmaceutically acceptable salts or tautomers thereof, R^{2c} and $R^{2c'}$ are C_{1-6} alkyl and H respectively. In some embodiments, R^{2c} and $R^{2c'}$ are C_{1-6} alkyl and H respectively, and R^{1c} and

$R^{1c'}$ are each H. In some embodiments, R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each C_{1-6} alkyl. In some embodiments, the compound of Formula (IC-O) is .

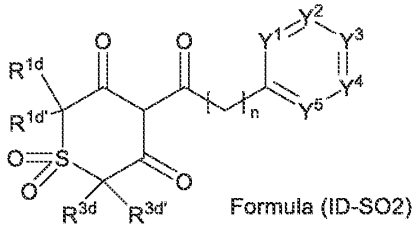
[0117] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (ID-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:


Formula (ID-O)

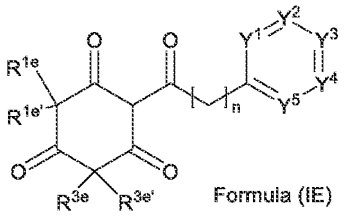
[0118] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (ID-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:


Formula (ID-S)

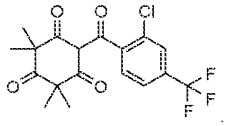
[0119] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (ID-SO2), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:


Formula (ID-SO2)

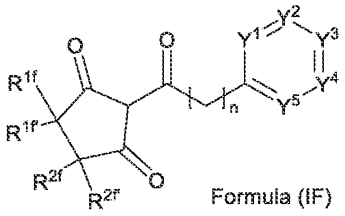
[0120] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IE)

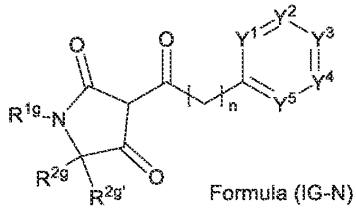
[0121] In some embodiments, R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each C_{1-6} alkyl. In some embodiments, the compound of Formula (IE) is .

[0122] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IF), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IF)

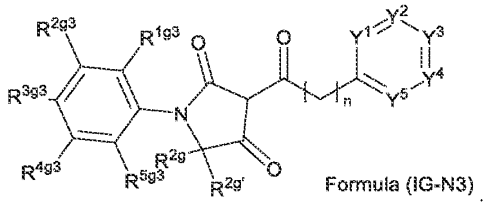
[0123] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IG-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG-N)

[0124] In some embodiments, the compound of Formula (IG-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IG-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In some embodiments, R^{1g} is C_{1-6} alkyl-aryl, wherein the C_{1-6} alkyl-aryl is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy. In some embodiments, the C_{1-6} alkyl-aryl is substituted with alkoxy (*e.g.*, -O-CH_3). In some embodiments, R^{1g} is -CH_2-aryl, wherein the -CH_2-aryl is unsubstituted or substituted with one or

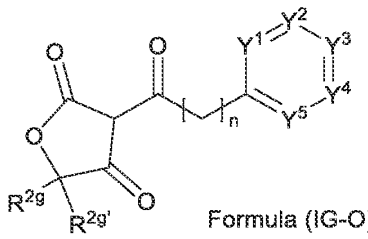
more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy. In some embodiments, the -CH_2-aryl is substituted with alkoxy (*e.g.*, -O-CH_3). In some embodiments, R^{1g} is -CH_2-C_6aryl, wherein the -CH_2-C_6aryl is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy. In some embodiments, the -CH_2-C_6aryl is substituted with alkoxy (*e.g.*, -O-CH_3). In some embodiments, R^{1g} is -CH_2-methoxybenzyl.



Formula (IG-N3)

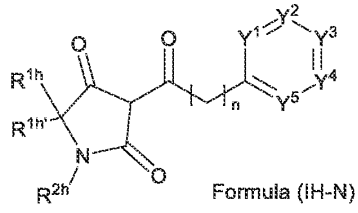
[0125] In some embodiments, the compound of Formula (I) or (IG-N) is a compound of Formula (IG-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are each H.

[0126] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IG-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



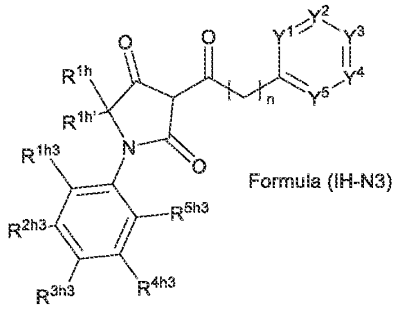
Formula (IG-O)

[0127] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IH-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-N)

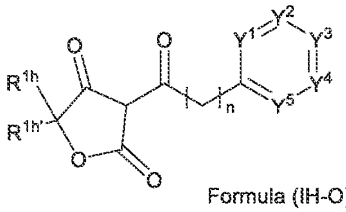
[0128] In some embodiments, the compound of Formula (IH-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IH-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-N3)

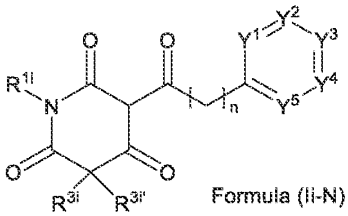
[0129] In some embodiments, the compound of Formula (I) or (IH-N) is a compound of Formula (IH-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each H.

[0130] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IH-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



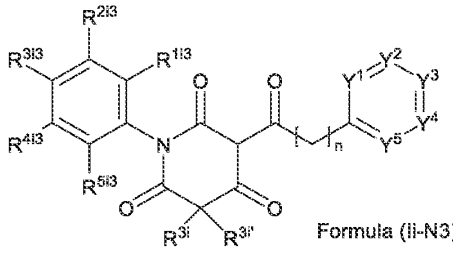
Formula (IH-O)

[0131] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (Ii-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (Ii-N)

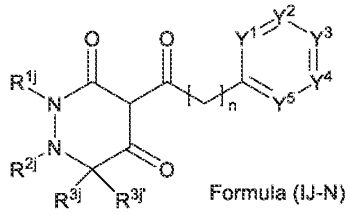
[0132] In some embodiments, the compound of Formula (Ii-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (Ii-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (Ii-N3)

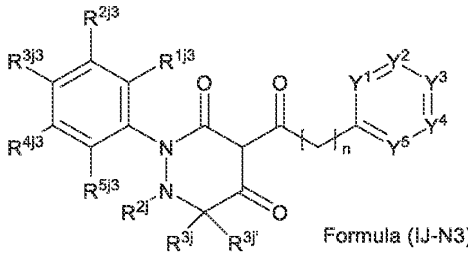
[0133] In some embodiments, the compound of Formula (I) or (Ii-N) is a compound of Formula (Ii-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1i3}, R^{2i3}, R^{3i3}, R^{4i3}, and R^{5i3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1i3}, R^{2i3}, R^{3i3}, R^{4i3}, and R^{5i3} are each H.

[0134] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IJ-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IJ-N)

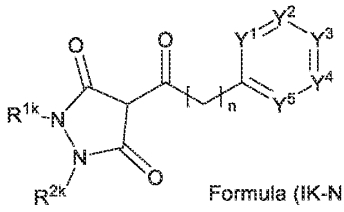
[0135] In some embodiments, the compound of Formula (IJ-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IJ-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IJ-N3)

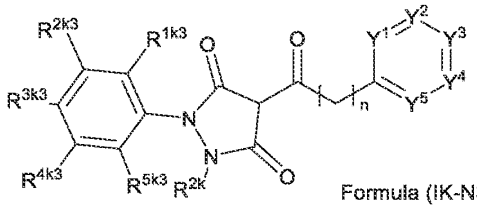
[0136] In some embodiments, the compound of Formula (I) or (IJ-N) is a compound of Formula (IJ-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1j3}, R^{2j3}, R^{3j3}, R^{4j3}, and R^{5j3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1j3}, R^{2j3}, R^{3j3}, R^{4j3}, and R^{5j3} are each H.

[0137] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IK-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IK-N)

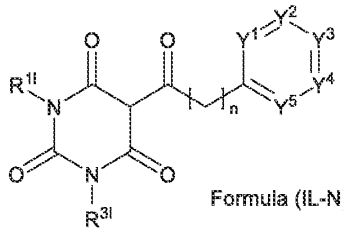
[0138] In some embodiments, the compound of Formula (IK-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IK-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IK-N3)

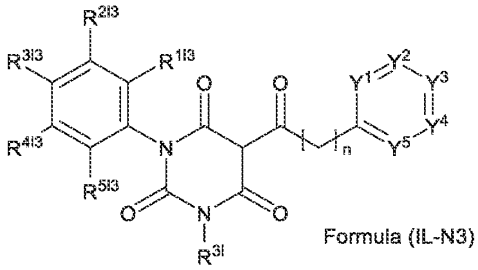
[0139] In some embodiments, the compound of Formula (I) or (IK-N) is a compound of Formula (IK-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1k3}, R^{2k3}, R^{3k3}, R^{4k3}, and R^{5k3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1k3}, R^{2k3}, R^{3k3}, R^{4k3}, and R^{5k3} are each H.

[0140] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IL-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IL-N)

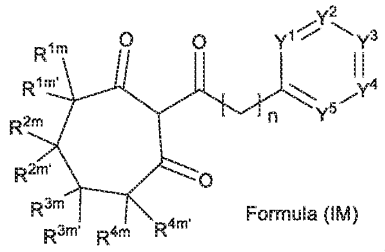
[0141] In some embodiments, the compound of Formula (IL-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IL-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IL-N3)

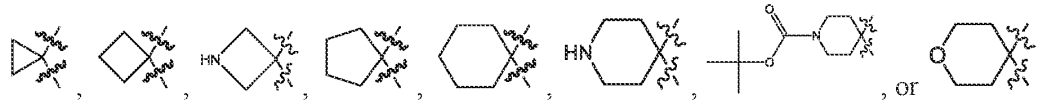
[0142] In some embodiments, the compound of Formula (I) or (IL-N) is a compound of Formula (IL-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1l3}, R^{2l3}, R^{3l3}, R^{4l3}, and R^{5l3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1l3}, R^{2l3}, R^{3l3}, R^{4l3}, and R^{5l3} are each H.

[0143] In some embodiments, the compound of Formula (I), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IM), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



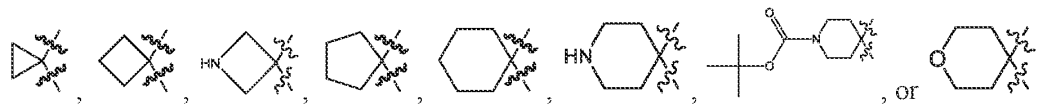
Formula (IM)

[0144] In some embodiments, R^{1a} and $R^{1a'}$, R^{2a} and $R^{2a'}$, R^{3a} and $R^{3a'}$, R^{2b} and $R^{2b'}$, R^{3b} and $R^{3b'}$, R^{1e} and $R^{1e'}$, R^{3e} and $R^{3e'}$, R^{1f} and $R^{1f'}$, R^{2f} and $R^{2f'}$, R^{1m} and $R^{1m'}$, R^{2m} and $R^{2m'}$, R^{3m} and $R^{3m'}$, or R^{4m} and $R^{4m'}$, when combined to form a cycloalkyl ring or heterocyclic ring, form



, or

[0145] In some embodiments, R^{1a} and $R^{1a'}$, R^{2a} and $R^{2a'}$, R^{3a} and $R^{3a'}$, R^{2b} and $R^{2b'}$, R^{3b} and $R^{3b'}$, R^{1c} and $R^{1c'}$, R^{2e} and $R^{2e'}$, R^{1d} and $R^{1d'}$, R^{3d} and $R^{3d'}$, R^{1e} and $R^{1e'}$, R^{3e} and $R^{3e'}$, R^{1f} and $R^{1f'}$, R^{2f} and $R^{2f'}$, R^{2g} and $R^{2g'}$, R^{1h} and $R^{1h'}$, R^{3i} and $R^{3i'}$, R^{3j} and $R^{3j'}$, R^{1m} and $R^{1m'}$, R^{2m} and $R^{2m'}$, R^{3m} and $R^{3m'}$, or R^{4m} and $R^{4m'}$, when combined to form a cycloalkyl ring or heterocyclic ring, form



, or

[0146] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O),

(IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), and (IM), or the pharmaceutically acceptable salts or tautomers thereof, n is 0. In some embodiments, n is 1.

[0147] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), and (IM), or the pharmaceutically acceptable salts or tautomers thereof, Y^1 is $C(NO_2)$.

[0148] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), and (IM), or the pharmaceutically acceptable salts or tautomers thereof, Y^1 is C(Cl).

[0149] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), and (IM), or the pharmaceutically acceptable salts or tautomers thereof, Y^1 is C(F).

[0150] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), and (IM), or the pharmaceutically acceptable salts or tautomers thereof, Y^3 is $C(CF_3)$.

[0151] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IH-N), (IH-N3), and (IH-O), or the pharmaceutically acceptable salts or tautomers thereof, R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3. In some embodiments, R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each H.

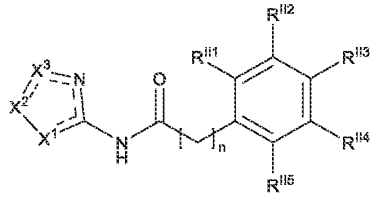
[0152] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (IF), (IG-N), (IG-N3), and (IG-O), or the pharmaceutically acceptable salts or tautomers thereof, R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each CH_3. In some embodiments, R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each H.

[0153] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (IF), (IG-N), (IG-N3), and (IG-O), or the pharmaceutically acceptable salts or tautomers thereof, R^{2a} and $R^{2a'}$ are CH_3 and H respectively, R^{2b} and $R^{2b'}$ are

CH_3 and H respectively, R^{2c} and $R^{2c'}$ are CH_3 and H respectively, R^{2f} and $R^{2f'}$ are CH_3 and H respectively, or R^{2g} and $R^{2g'}$ are CH_3 and H respectively.

[0154] In some embodiments of the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (ID-O), (ID-S), (ID-SO2), (IE), (Ii-N), (Ii-N3), (IJ-N), and (IJ-N3), or the pharmaceutically acceptable salts or tautomers thereof, R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each CH_3. In some embodiments, R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each H.

[0155] In some embodiments, the disclosure provides a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

X^1 is NR^1, X^2 is CR^2, and X^3 is N or CH;

X^1 is O, X^2 is CR^2, and X^3 is N;

X^1 is N, X^2 is NR^1, and X^3 is N; or

X^1 is NR^3, X^2 is N, and X^3 is N;

n is 0 or 1;

R^1 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^1 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^2 is selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, SO_2-C_{1-6} alkyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

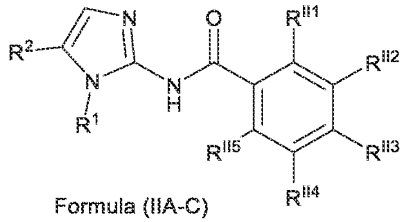
wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is selected from C_{4-6} alkyl, cycloalkyl, aryl substituted with one or more substituents selected from the group consisting of halo and methyl, benzyl substituted with one or more F, and heteroaryl;

R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

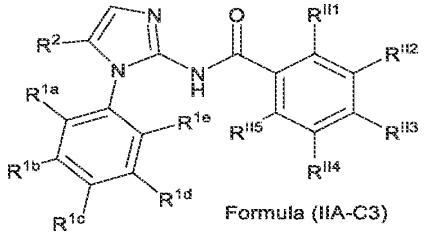
[0156] In some embodiments, X^1 is NR^1, X^2 is CR^2, and X^3 is N or CH. In some embodiments, X^1 is O, X^2 is CR^2, and X^3 is N. In some embodiments, X^1 is N, X^2 is NR^1, and X^3 is N. In some embodiments, X^1 is NR^3, X^2 is N, and X^3 is N.

[0157] In some embodiments, the compound of Formula (II), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIA-C), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



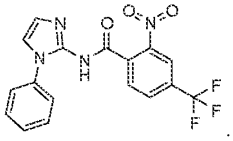
Formula (IIA-C)

[0158] In some embodiments, the compound of Formula (IIA-C), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIA-C3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

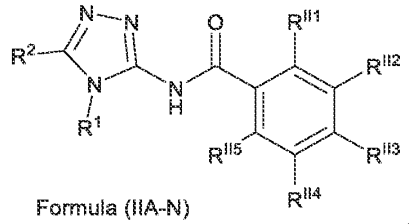


Formula (IIA-C3)

[0159] In some embodiments, the compound of Formula (II) or (IIA-C) is a compound of Formula (IIA-C3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each H. In some embodiments, the compound of Formula (IIA-C3) is

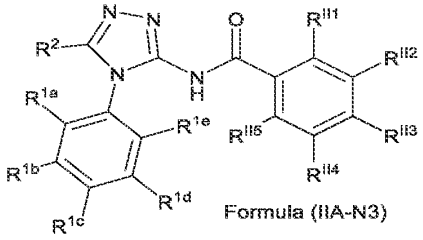


[0160] In some embodiments, the compound of Formula (II), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIA-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N)

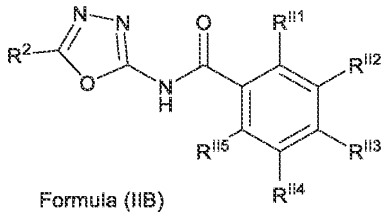
[0161] In some embodiments, the compound of Formula (IIA-N), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIA-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N3)

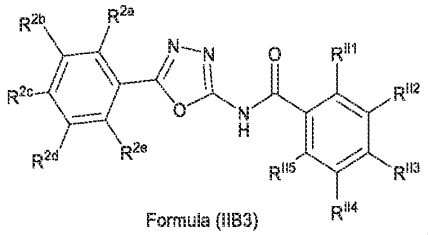
[0162] In some embodiments, the compound of Formula (II) or (IIA-N) is a compound of Formula (IIA-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each H.

[0163] In some embodiments, the compound of Formula (II), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIB), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIB)

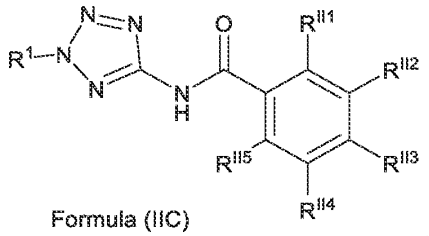
[0164] In some embodiments, the compound of Formula (IIB), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIB3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIB3)

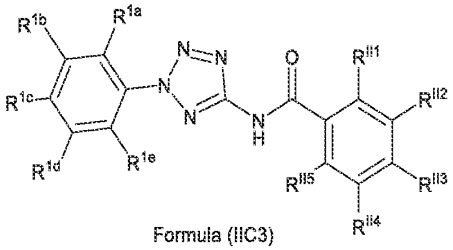
[0165] In some embodiments, the compound of Formula (II) or (IIB) is a compound of Formula (IIB3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each H.

[0166] In some embodiments, the compound of Formula (II), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIC), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIC)

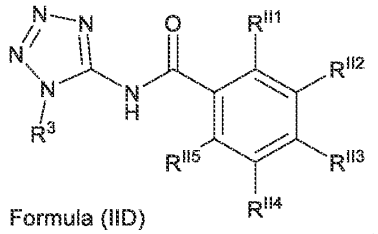
[0167] In some embodiments, the compound of Formula (IIC), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IIC3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIC3)

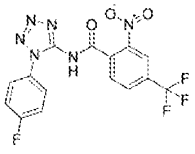
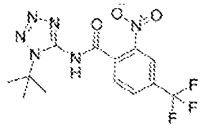
[0168] In some embodiments, the compound of Formula (II) or (IIC) is a compound of Formula (IIC3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each H. In some embodiments, one of R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} is halo, and each of the others is H. In some embodiments, R^{1c} is F, and R^{1a}, R^{1b}, R^{1d}, and R^{1e} are each H.

[0169] In some embodiments, the compound of Formula (II), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IID), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IID)

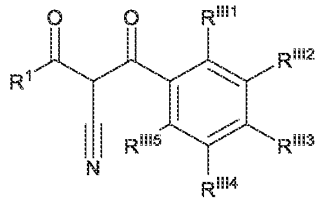
[0170] In some embodiments, the compound of Formula (II) is a compound of Formula (IID), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^3 is C_{4-6} alkyl or phenyl substituted with one or more halo. In some embodiments, R^3 is phenyl substituted with F. In some embodiments, R^3 is phenyl substituted with one instance of F. In some embodiments, R^3 is C_4 alkyl. In some embodiments, R^3 is tert-butyl.

[0171] In some embodiments, the compound of Formula (IID) is . In some embodiments, the compound of Formula (IID) is .

[0172] In some embodiments of the compounds of Formulae (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), and (IID), or the pharmaceutically acceptable salts or tautomers thereof, R^{II1} is H or NO_2. In some embodiments, R^{II1} is H. In some embodiments, R^{II1} is NO_2.

[0173] In some embodiments of the compounds of Formulae (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), and (IID), or the pharmaceutically acceptable salts or tautomers thereof, R^{II3} is H or CF_3. In some embodiments, R^{II3} is H. In some embodiments, R^{II3} is CF_3.

[0174] In some embodiments, the disclosure provides a compound of Formula (III):



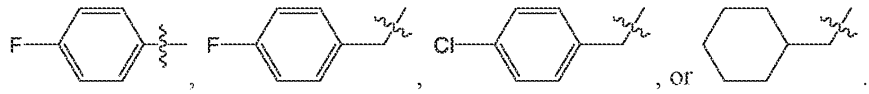
Formula (III)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

R^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, and C_1 alkyl-heteroaryl;

wherein the C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, or C_1 alkyl-heteroaryl of R^1 is unsubstituted or substituted with halo;

R^{III1}, R^{III2}, R^{III3}, R^{III4}, and R^{III5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

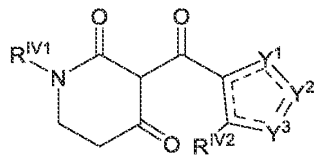
[0175] In some embodiments of the compounds of Formula (III), or the pharmaceutically acceptable salts or tautomers thereof, R^1 is aryl or C_1 alkyl-aryl, wherein the aryl or C_1 alkyl-aryl may be unsubstituted or substituted with one or more halo. In some embodiments, R^1 is cycloalkyl or C_1 alkyl-cycloalkyl, wherein the cycloalkyl or C_1 alkyl-cycloalkyl may be unsubstituted or substituted with one or more halo. In some embodiments, R^1 is phenyl substituted with one or more F. In some embodiments, R^1 is benzyl substituted with one or more F. In some embodiments, R^1 is benzyl substituted with one or more Cl. In some embodiments, R^1 is .

[0176] In some embodiments of the compounds of Formula (III), or the pharmaceutically acceptable salts or tautomers thereof, R^{III1} is H or NO_2. In some embodiments, R^{III1} is H. In some embodiments, R^{III1} is NO_2.

[0177] In some embodiments of the compounds of Formula (III), or the pharmaceutically acceptable salts or tautomers thereof, R^{III2} is H, halo, or SO_2-C_{1-6} alkyl. In some embodiments, R^{III2} is H. In some embodiments, R^{III2} is halo. In some embodiments, R^{III2} is SO_2-C_{1-6} alkyl.

[0178] In some embodiments of the compounds of Formula (III), or the pharmaceutically acceptable salts or tautomers thereof, R^{III3} is H or CF_3. In some embodiments, R^{III3} is H. In some embodiments, R^{III3} is CF_3.

[0179] In some embodiments, the disclosure provides a compound of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

Y^1 is CR^1, Y^2 is N, and Y^3 is NR^3;

Y^1 is CR^1, Y^2 is O or S, and Y^3 is CR^3;

Y^1 is N, Y^2 is CR^2, and Y^3 is O or S; or

Y^1 is O or S, Y^2 is CR^2, and Y^3 is CR^3;

R^1 and R^2 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^1 or R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^3 combines with R^{IV2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{IV1} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{IV1} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

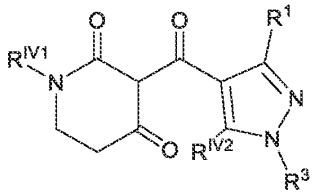
R^{IV2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

R^{IV2} combines with R^3 to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more

substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl.

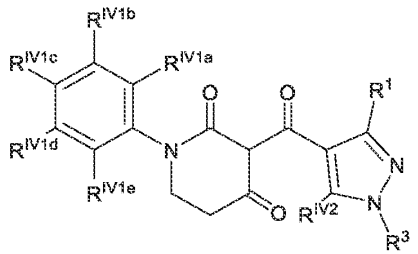
[0180] In some embodiments, R^3 and R^{IV2} combine to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring. In some embodiments, R^3 and R^{IV2} combine to form a C_{6-10} aryl ring. In some embodiments, R^3 and R^{IV2} combine to form a heteroaryl ring comprising 4 to 8 carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, R^3 and R^{IV2} combine to form a C_{3-6} cycloalkyl ring. In some embodiments, R^3 and R^{IV2} combine to form a C_{3-8} cycloalkyl ring. In some embodiments, R^3 and R^{IV2} combine to form a heterocyclic ring comprising 3 to 8 carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen, and sulfur. In some embodiments, R^3 and R^{IV2} combine to form .

[0181] In some embodiments, the compound of Formula (IV), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVA)

[0182] In some embodiments, the compound of Formula (IVA), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

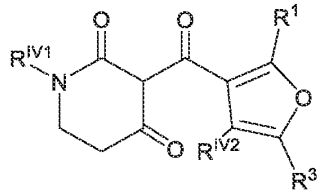


Formula (IVA3)

[0183] In some embodiments, the compound of Formula (IV) or (IVA) is a compound of Formula (IVA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6}

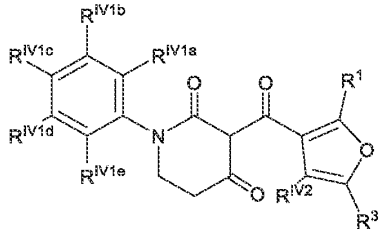
haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{IV1c} is F, and R^{IV1a}, R^{IV1b}, R^{IV1d}, and R^{IV1e} are each H. In some embodiments, R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

[0184] In some embodiments, the compound of Formula (IV), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O)

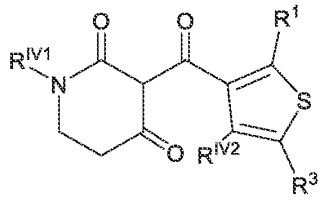
[0185] In some embodiments, the compound of Formula (IVB-O), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVB-O3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O3)

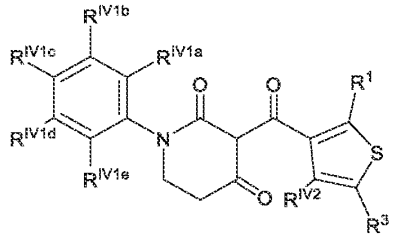
[0186] In some embodiments, the compound of Formula (IV) or (IVB-O) is a compound of Formula (IVB-O3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{IV1c} is F, and R^{IV1a}, R^{IV1b}, R^{IV1d}, and R^{IV1e} are each H. In some embodiments, R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

[0187] In some embodiments, the compound of Formula (IV), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVB-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S)

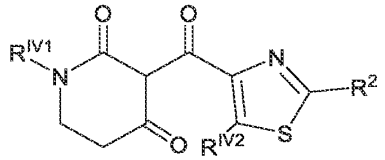
[0188] In some embodiments, the compound of Formula (IVB-S), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVB-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S3)

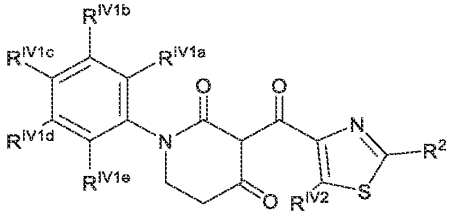
[0189] In some embodiments, the compound of Formula (IV) or (IVB-S) is a compound of Formula (IVB-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

[0190] In some embodiments, the compound of Formula (IV), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVC-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S)

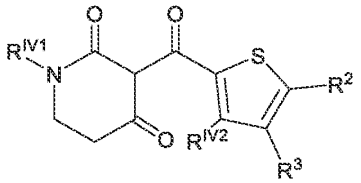
[0191] In some embodiments, the compound of Formula (IVC-S), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVC-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S3)

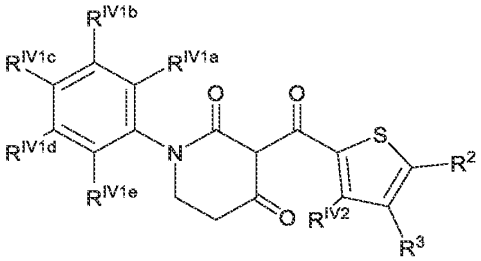
[0192] In some embodiments, the compound of Formula (IV) or (IVC-S) is a compound of Formula (IVC-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{IV1c} is F, and R^{IV1a}, R^{IV1b}, R^{IV1d}, and R^{IV1e} are each H. In some embodiments, R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

[0193] In some embodiments, the compound of Formula (IV), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVD), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD)

[0194] In some embodiments, the compound of Formula (IVD), or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is a compound of Formula (IVD3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD3)

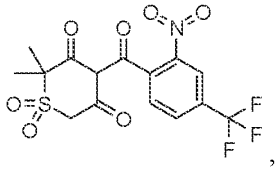
[0195] In some embodiments, the compound of Formula (IV) or (IVD) is a compound of Formula (IVD3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl. In some embodiments, R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

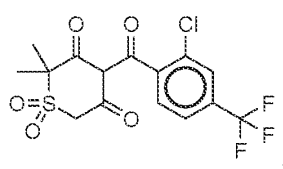
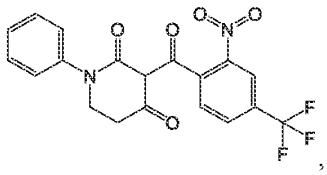
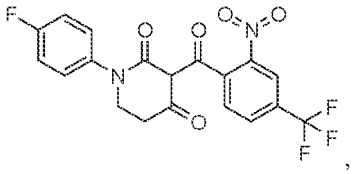
[0196] In some embodiments of the compounds of Formulae (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), and (IVB-S3), or the pharmaceutically acceptable salts or tautomers thereof, R^1 is H or CF_3. In some embodiments, R^1 is H. In some embodiments, R^1 is CF_3.

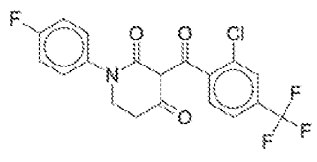
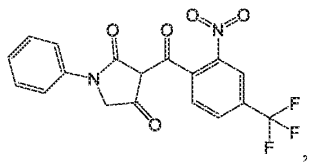
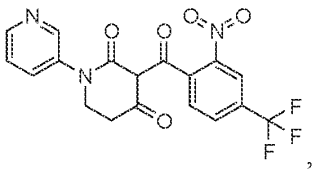
[0197] In some embodiments of the compounds of Formulae (IV), (IVC-S), (IVC-S3), (IVD), and (IVD3), or the pharmaceutically acceptable salts or tautomers thereof, R^2 is H or CF_3. In some embodiments, R^2 is H. In some embodiments, R^2 is CF_3.

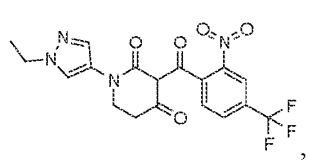
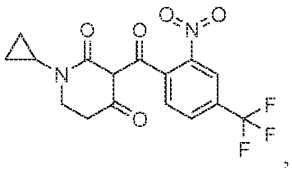
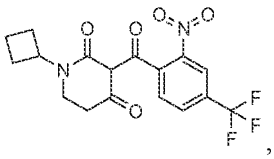
[0198] In some embodiments of the compounds of Formulae (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVD), and (IVD3), or the pharmaceutically acceptable salts or tautomers thereof, R^3 is H or C_{1-6} alkyl. In some embodiments, R^3 is H. In some embodiments, R^3 is C_{1-6} alkyl.

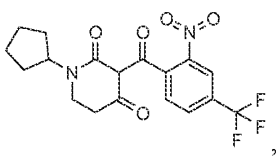
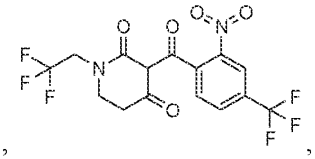
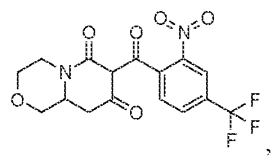
[0199] In some embodiments, the compound, or the pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, is selected from the group consisting of the following Table 1 compounds: Compound Nos. 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 110, 111, 112, 113, 114, 116, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, and pharmaceutically acceptable salt and tautomers of any of the foregoing.

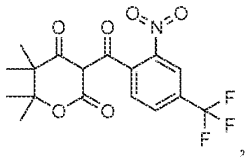
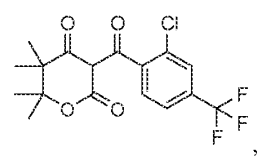
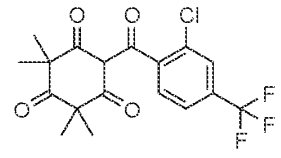
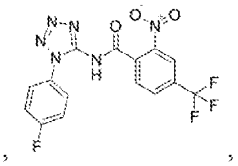
[0200] In some embodiments, the compound is ,

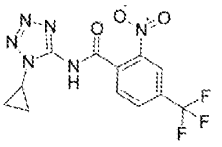
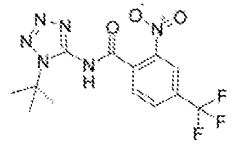
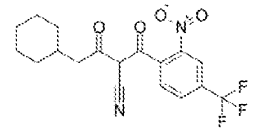
, , ,

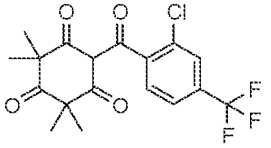
, , ,

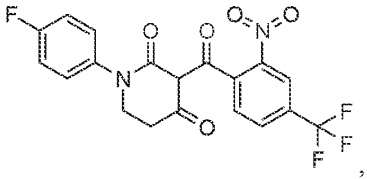
, , ,

, , ,

, , , ,

, , or , or a pharmaceutically acceptable salt or tautomer of any of the foregoing. In some embodiments, the compound is

, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

In some embodiments, the compound is , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0201] The present disclosure also provides a pharmaceutical composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, and a pharmaceutically acceptable carrier.

[0202] Unless otherwise stated, structures depicted herein are also meant to include pharmaceutically acceptable salts, tautomers, and stereoisomers thereof. Accordingly, embodiments of the present disclosure are directed to compounds and methods of using

compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salts, tautomers, and stereoisomers thereof. Moreover, reference to compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salts and tautomers thereof is considered to include reference to stereoisomers of any thereof.

[0203] In some embodiments, the compound is a stereoisomer of a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0204] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically-enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by deuterium or tritium, the replacement of a carbon atom by ^{13}C or ^{14}C, the replacement of a nitrogen atom by ^{15}N, or the replacement of an oxygen atom by ^{17}O or ^{18}O are within the scope of the present disclosure. Such isotopically-labeled compounds are useful as research or diagnostic tools.

[0205] "Alkyl," as used herein, refers to an unbranched or branched saturated hydrocarbon chain. In some embodiments, alkyl as used herein has 1 to 6 carbon atoms (C_{1-6} alkyl.) In some embodiments, C_{1-6} alkyl refers to a group with 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, alkyl as used herein has 2 to 6 carbon atoms (C_{2-6}alkyl). In some embodiments, C_{2-6}alkyl refers to a group with 2, 3, 4, 5, or 6 carbon atoms. Examples of alkyl groups include

methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methyl pentyl. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed. Thus, for example, "butyl" can include n-butyl, sec-butyl, isobutyl and t-butyl, and "propyl" can include n-propyl and isopropyl. In some embodiments, an alkyl (*e.g.*, C_{1-6} alkyl) is bound to another atom to form an ether (*e.g.*, -O-C_{1-6} alkyl), an ester (*e.g.*, -CO(O)-C_{1-6} alkyl), an aryl attached via the alkyl (*e.g.*, -C_{1-6} alkyl-aryl), an aryl substituted with an alkyl (*e.g.*, -aryl-C_{1-6} alkyl), a heteroaryl attached via the alkyl (*e.g.*, -C_{1-6} alkyl-heteroaryl), a heteroaryl substituted with an alkyl (*e.g.*, -heteroaryl-C_{1-6} alkyl).

[0206] "Alkoxy," as used herein, refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "O" in the chain, *i.e.*, -O(alkyl). In some embodiments, alkyl as used herein has 1 to 6 carbon atoms (-O-C_{1-6} alkyl.) In some embodiments, -O-C_{1-6} alkyl refers to a group with 1, 2, 3, 4, 5, or 6 carbon atoms. Examples of alkoxy groups include, without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

[0207] "Cycloalkyl" or "cycloalkyl ring," as used herein, refers to a saturated or partially saturated, monocyclic, fused or spiro polycyclic, carbocycle having from 3 to 18 carbon atoms per ring. In some embodiments, the cycloalkyl is a saturated, monocyclic carbocycle. In some embodiments, the cycloalkyl has 3 to 6 carbon atoms (C_{3-6} cycloalkyl.) In some embodiments, C_{3-6} cycloalkyl refers to a group with 3, 4, 5, or 6 carbon atoms. In some embodiments, the C_{3-6} cycloalkyl is a saturated, monocyclic carbocycle having 3 to 6 (*i.e.*, 3, 4, 5, or 6) carbon atoms. In some embodiments, the cycloalkyl is a saturated, monocyclic carbocycle. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, and cyclooctanyl. In some embodiments, C_{3-6} cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0208] "Aryl" or "aryl ring," as used herein, refers to a monocyclic or polycyclic group having at least one hydrocarbon aromatic ring wherein all of the ring atoms of the at least one hydrocarbon aromatic ring are carbon. Aryl may include groups with a single aromatic ring (*e.g.*, phenyl) and multiple fused aromatic rings (*e.g.*, naphthyl, anthryl). Aryl may further include groups with one or more aromatic hydrocarbon rings fused to one or more non-aromatic hydrocarbon rings (*e.g.*, fluorenyl; 2,3-dihydro-1H-indene; 1,2,3,4-tetrahydronaphthalene). In some embodiments, aryl as used herein has from 6 to 14 (6, 7, 8, 9, 10, 11, 12, 13, or 14) carbon

atoms ($(C_6$-$C_{14})$aryl), or 6 to 10 (6, 7, 8, 9, or 10) carbon atoms ($(C_6$-$C_{10})$aryl). Where the aryl includes fused rings, the aryl may connect to one or more substituents or moieties of the Formulae described herein through any atom of the fused ring for which valency permits. In some embodiments, the aryl has 6 carbon atoms (C_6aryl). In some embodiments, the aryl is a phenyl.

[0209] "Heteroaryl" or "heteroaryl ring," as used herein, refers to a monocyclic or polycyclic group comprising at least one aromatic ring, wherein the aromatic ring comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S. The heteroaryl group may comprise 5, 6, 7, 8, 9, 10, 11, 12, or more ring atoms, where ring atoms refer to the sum of carbon and heteroatoms in the one or more rings (*e.g.*, be a 5-membered, 6-membered, 7-membered, 8-membered, 9-membered, 10-membered, 11-membered, or 12-membered heteroaryl). In some embodiments, heteroaryl includes groups with an aromatic ring that comprises at least one ring heteroatom independently selected from the group consisting of N, O, and S, (*e.g.*, pyridinyl, pyrazinyl, furanyl, thiophenyl). In certain embodiments, heteroaryl includes polycyclic groups with an aromatic ring comprising at least one ring heteroatom, fused to a non-aromatic hydrocarbon ring (*e.g.*, 5,6,7,8-tetrahydroquinolinyl; 4,5,6,7-tetrahydroisobenzofuranyl). In some embodiments, heteroaryl includes polycyclic groups with an aromatic ring comprising at least one ring heteroatom fused to an aromatic hydrocarbon ring (*e.g.*, quinolinyl, quinoxalinyl, benzothiazolyl). In still further embodiments, heteroaryl includes polycyclic groups with two fused aromatic rings, wherein each ring comprises at least one ring heteroatom (*e.g.*, naphthyridinyl). Heteroaryl may include groups comprising 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 or 2 ring heteroatoms, or 1 ring heteroatom, wherein each ring heteroatom is independently selected from the group consisting of N, O, and S. In one example, a heteroaryl has 3 to 8 ring carbon atoms, with 1 to 3 ring heteroatoms independently selected from N, O, and S. Examples of heteroaryl groups include, without limitations, pyridyl, pyridazinyl, pyrimidinyl, benzothiazolyl, and pyrazolyl.

[0210] "Heterocycle" or "heterocyclic ring," as used herein, refers to a saturated or partially unsaturated and non-aromatic monocyclic or fused or spiro polycyclic ring structure of 4 to 18 atoms containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur wherein there is not delocalized π-electrons (aromaticity) shared among the ring carbon or heteroatoms. Examples of heterocyclic rings include, but are not limited to, imidazolidin-2-one, oxadiazole (*e.g.*, 1,2,5-oxadiazole), oxetane, azetidine, tetrahydrofuran, pyrrolidine, oxazoline, oxazolidine,

thiazoline, thiazolidine, pyran, thiopyran, tetrahydropyran, dioxane, piperidine, morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, piperazine, azepine, oxepine, diazepine, dihydrothiophen-2(3H)-one, tetrahydrothiophene 1,1-dioxide, 2,5-dihydro-1H-pyrrole, imidazolidin-2-one, pyrrolidin-2-one, dihydrofuran-2(3H)-one, 1,3-dioxolan-2-one, isothiazolidine-1,1-dioxide, 4,5-dihydro-1H-imidazole, 4,5-dihydrooxazole, oxirane, pyrazolidine, 4H-1,4-thiazine, thiomorpholine, 1,2,3,4-tetrahydropyridine, 1,2,3,4-tetrahydropyrazine, 1,3-oxazinan-2-one, tetrahydro-2H-thiopyran 1,1-dioxide, 7-oxabicyclo[2.2.1]heptane, 1,2-thiazepane-1,1-dioxide, octahydro-2H-quinolizinyl, 1,3-diazabicyclo[2.2.2]octane, 2,3-dihydrobenzo[b][1,4]dioxine, 3-azabicyclo[3.2.1]octane, 8-azaspiro[4.5]decane, 8-oxa-3-azabicyclo[3.2.1]octane, 2-azabicyclo[2.2.1]heptane, 2,8-diazaspiro[5.5]undecane, 2-azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane, decahydroisoquinoline, 1-oxa-8-azaspiro[4.5]decane, 8-azabicyclo[3.2.1]octane, 1,4'-bipiperidine, azepane, 8-oxa-3-azabicyclo[3.2.1]octane, 3,4-dihydro-2H-benzo[b][1,4]oxazine, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine, 1,4-diazepane, phenoxathiine, benzo[d][1,3]dioxole, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxine, 4-(piperidin-4-yl)morpholinyl, 3-azaspiro[5.5]undecane, decahydroquinoline, piperazin-2-one, 1-(pyrrolidin-2-ylmethyl)pyrrolidine, 1,3'-bipyrrolidine, and 6,7,8,9-tetrahydro-1H,5H-pyrazolo[1,2-a][1,2]diazepine. In some embodiments, the heterocyclic ring is imidazolidin-2-one. In some embodiments, the heterocyclic ring is oxadiazole (*e.g.*, 1,2,5-oxadiazole).

[0211] As used herein, the term "substituted" means that the specified group or moiety bears one or more suitable substituents wherein the substituents may connect to the specified group or moiety at one or more positions. For example, an aryl substituted with a cycloalkyl may indicate that the cycloalkyl connects to one atom of the aryl with a bond or by fusing with the aryl and sharing two or more common atoms.

[0212] As used herein, the term "unsubstituted" means that the specified group bears no substituents.

[0213] "Halo," as used herein, refers to fluoro, chloro, bromo, or iodo radicals.

[0214] "Haloalkyl," as used herein, refers to an alkyl group (*e.g.*, C_{1-6} alkyl) substituted with one more halogen (*e.g.*, fluoro, chloro, bromo, or iodo radicals.)

[0215] In some embodiments, haloalkyl has 1 to 6 carbon atoms (C_{1-6} haloalkyl) substituted with one more halogen (*e.g.*, fluoro, chloro, bromo, or iodo radicals.) In some embodiments, C_{1-6} haloalkyl refers to a group with 1, 2, 3, 4, 5, or 6 carbon atoms substituted with 1, 2, 3, or more

halogen (*e.g.*, fluoro, chloro, bromo, or iodo radicals.) In some embodiments, the halogen is fluoro. In some embodiments, the halogen is chloro. In some embodiments, the halogen is bromo. Examples of C_{1-6} haloalkyl include, but are not limited to, trifluoromethyl (CF_3).

[0216] It should be understood that when a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C_{1-6} alkyl" (which may also be referred to as C1-C6 alkyl, C_1-C_6 alkyl, or C_{1-6} alkyl) is intended to encompass C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0217] It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

[0218] It should be understood that all geometric isomeric forms are included within the present disclosure, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans- configuration.

[0219] The compounds of the various Formulae may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the various Formulae as well as mixtures thereof, including racemic mixtures, form part of the present disclosure. In addition, the present disclosure embraces all geometric isomers. For example, if a compound of the various Formulae incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the present disclosure. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic or enantiomerically pure form, or any other form in terms of stereochemistry. The assay results may reflect the data collected for the racemic form, the enantiomerically pure form, or any other form in terms of stereochemistry.

[0220] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically-active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers, and converting (*e.g.*, hydrolyzing) the

individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the various Formulae may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of the present disclosure. Enantiomers can also be separated by use of a chiral HPLC column.

[0221] In some embodiments, the compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) and pharmaceutically acceptable salts or tautomers of any of the foregoing are enantiomers. In some embodiments, the compounds or pharmaceutically acceptable salts or tautomers thereof are the (*S*)-enantiomer. In other embodiments the compounds or pharmaceutically acceptable salts or tautomers thereof are the (*R*)-enantiomer. In some embodiments, the compounds or pharmaceutically acceptable salts or tautomers thereof are the (+) enantiomer or (-) enantiomer.

[0222] Some embodiments are directed to isotopically-labelled compounds of the present disclosure which are identical to those recited herein but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H (or D), ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

[0223] Certain isotopically-labelled compounds of the various Formulae (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced-dosage requirements) and hence may be preferred in some circumstances. Isotopically-labelled compounds of the various Formulae can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below by substituting an appropriate isotopically-labelled reagent for a nonisotopically-labelled reagent.

[0224] The compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII), and pharmaceutically acceptable salts or tautomers of any of the foregoing may form salts which are also within the scope of the present disclosure. Reference to a compound of the Formula herein is understood to include reference to salts thereof, unless otherwise indicated.

[0225] The present disclosure is directed to compounds as described herein and pharmaceutically acceptable salts or tautomers thereof. The present disclosure is also directed to pharmaceutical compositions comprising one or more compounds as described herein or pharmaceutically acceptable salts or tautomers thereof.

[0226] "Pharmaceutically acceptable," as used herein, refers to that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and not biologically or otherwise undesirable, and includes that which is acceptable for veterinary use as well as human pharmaceutical use. For example, provided herein is a pharmaceutical composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII) or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, and a pharmaceutically acceptable excipient.

[0227] "Pharmaceutically acceptable salt," as used herein, refers to a salt which is generally safe, non-toxic and not biologically or otherwise undesirable, and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

[0228] In some embodiments, a compound of the disclosure inhibits HPD. In some embodiments, a compound of the disclosure comprises no or minimal inhibitory activity for SPR (*e.g.*, selectively inhibits HPD over SPR).

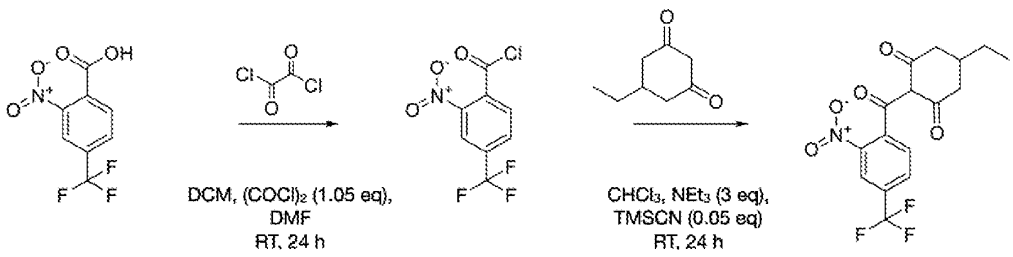
Methods of Synthesizing the Compounds

[0229] The compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3),

(IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salts or tautomers thereof may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic scheme and in light of the teaching provided herein. In the scheme described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, which is hereby incorporated by reference in its entirety). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of the disclosed compounds (*e.g.*, Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salt, stereoisomer, or tautomer thereof).

[0230] The compounds described in this patent were synthesized using the following general scheme shown on compound 1 as an example. This synthetic approach was described in detail before for nitisinone (WO2015101794A1, which is hereby incorporated by reference in its entirety). Briefly, the compounds were synthesized by a two-step reaction in which an appropriate benzoic acid (or analogue as required) was used to prepare its acyl chloride. In the second step, the acyl chloride was reacted with the appropriate 1,3-diketone in alcohol-free chloroform. In step 2 of the reaction, 1,3-diketone reacts with acyl chloride in the presence of triethylamine to give an unstable O-alkyl intermediate, which converts into the final product using a catalytic amount of trimethylsilylcyanide. The final product was obtained using an acid-base extraction and further purified by HPLC. The general reaction scheme is given using compound 1 as an example. Any changes to the procedure used for specific products as well as synthesis of precursors where they were not available are described in detailed examples below.

Scheme 1: General Synthetic Scheme



Those skilled in the art will recognize if a stereocenter exists in the disclosed compounds (*e.g.*, Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salt, stereoisomer, or tautomer thereof). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994), which is hereby incorporated by reference in its entirety.

[0231] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

[0232] Compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII) and pharmaceutically acceptable salts or tautomers thereof can be prepared according to procedures outlined in Schemes and Examples herein. In the Examples section, compounds of

the present disclosure are further exemplified by specific examples. Unless otherwise specified, all temperatures were expressed in °C and all reactions are conducted at room temperature.

Pharmaceutical Compositions

[0233] The compounds of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), (VIII), and pharmaceutically acceptable salts or tautomers of the foregoing may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the disclosed compound or pharmaceutically acceptable salts or tautomers thereof is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988, which is hereby incorporated by reference in its entirety.

[0234] The term "pharmaceutically acceptable carrier," as used herein, encompasses one or more carriers, excipients, and diluents and refers to a material, composition, or vehicle such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body, of a subject. Excipients should be selected on the basis of compatibility and the release profile properties of the desired dosage form. Exemplary pharmaceutically acceptable carriers include, *e.g.*, binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, spray-dried dispersions, and the like.

[0235] The present disclosure provides a pharmaceutical composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or a

pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, and a pharmaceutically acceptable carrier.

[0236] The present disclosure also provides a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, for use in medicine.

[0237] The present disclosure also provides a pharmaceutical composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0238] The present disclosure further provides a process for the preparation of a pharmaceutical composition of the present disclosure which comprises mixing a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing, with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0239] Depending on the mode of administration, the pharmaceutical composition will comprise from about 0.05 to about 99 %w (per cent by weight), more particularly from about 0.05 to about 80 %w, still more particularly from about 0.10 to about 70 %w, and even more particularly from about 0.10 to about 50 %w, of active ingredient, all percentages by weight being based on total composition.

[0240] Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are liquids in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for example, in combination with a preservative. Formulations for parenteral injection can be presented in unit dosage form, for example, in ampoules, or in multi-dose containers with a preservative.

Methods of Treatment

[0241] In some embodiments, disclosed herein is a method of treating a condition (e.g., a condition that is responsive to modulation or inhibition of HPD, for example, tyrosinemia), the method comprising administering to a subject in need thereof a therapeutically effective amount of an HPD inhibitor with no or minimal off-target inhibitory activity for SPR. In some embodiments, the HPD inhibitor is a selective HPD inhibitor.

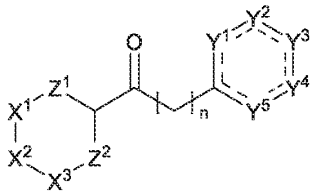
[0242] The terms "treat," "treating," or "treatment," as used herein, refer to any indicia of success in the amelioration of a disorder (such as injury, disease pathology, or condition), including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disorder more tolerable to the subject; slowing or stopping the rate of degeneration, decline, or development; slowing the progression of disorder; making the final point of degeneration less debilitating; improving a subject's physical or mental well-being; or relieving or causing regression of the disorder. The treatment of symptoms, including the amelioration of symptoms, can be based on objective or subjective parameters, which may include the results of a physical examination, a neuropsychiatric exam, and/or a psychiatric evaluation.

[0243] The terms "administered," "administration," or "administering," as used herein, refer to either directly administering a disclosed compound or pharmaceutically acceptable salt, stereoisomer, or tautomer of the disclosed compound or a composition to a subject, including an animal, in need of treatment by bringing such individual in contact with, or otherwise exposing such individual to, such compound.

[0244] As used herein, the term "subject" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the class Mammalia:

humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the present disclosure, the mammal is a human.

[0245] In some embodiments, the disclosure provides a compound of Formula (V). In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all === together form an aryl ring or heteroaryl ring, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond;

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$;

X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$;

X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond;

X^1 is NR^{1l} or O, X^2 is C(O), and X^3 is NR^{3l} or O; or

X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$;

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl; wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3i} and $R^{3i'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3i} or $R^{3i'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3j} and $R^{3j'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3j} or $R^{3j'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{2h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1i} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1i} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1j} and R^{2j} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1j} or R^{2j} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1k} and R^{2k} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1k} or R^{2k} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, or CN;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$, then:

Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; or

Y^1 is C(O); Y^2 is $N(R^{2b2'})$; Y^3 is $C(R^{3b2'})$; Y^4 is $C(R^{4b2'})$; and Y^5 is N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic

ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN;

$R^{2b2'}$ is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

$R^{3b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

$R^{4b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

$R^{2b2'}$ combines with $R^{3b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{4b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{4b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

$R^{3b2'}$ combines with $R^{4b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{2b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4c2} combines with R^{5c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{3c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} is Cl; R^{2e2} is H, R^{3e2} is C_{1-6} haloalkyl, NO_2, or SO_2-C_{1-6} alkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} is NO_2; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic

ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$; then Y^1 is $C(R^{1i2})$ or N; Y^2 is $C(R^{2i2})$ or N; Y^3 is $C(R^{3i2})$ or N; Y^4 is $C(R^{4i2})$ or N; and Y^5 is $C(R^{5i2})$ or N; wherein

R^{1i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1i2} combines with R^{2i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2i2} combines with R^{3i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3i2} combines with R^{4i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4i2} combines with R^{5i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{3i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$; then Y^1 is $C(R^{1j2})$ or N; Y^2 is $C(R^{2j2})$ or N; Y^3 is $C(R^{3j2})$ or N; Y^4 is $C(R^{4j2})$ or N; and Y^5 is $C(R^{5j2})$ or N; wherein

R^{1j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1j2} combines with R^{2j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2j2} combines with R^{3j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3j2} combines with R^{4j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4j2} combines with R^{5j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{3j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond; then Y^1 is $C(R^{1k2})$ or N; Y^2 is $C(R^{2k2})$ or N; Y^3 is $C(R^{3k2})$ or N; Y^4 is $C(R^{4k2})$ or N; and Y^5 is $C(R^{5k2})$ or N; wherein

R^{1k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1k2} combines with R^{2k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{3k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2k2} combines with R^{3k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3k2} combines with R^{4k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4k2} combines with R^{5k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{3k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{11} or O, X^2 is C(O), and X^3 is NR^{31} or O; then Y^1 is $C(R^{112})$ or N; Y^2 is $C(R^{212})$ or N; Y^3 is $C(R^{312})$ or N; Y^4 is $C(R^{412})$ or N; and Y^5 is $C(R^{512})$ or N; wherein

R^{112} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{212} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{312} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{412} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{512} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{112} combines with R^{212} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{312}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{212} combines with R^{312} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{312} combines with R^{412} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{412} combines with R^{512} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{312} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

or

if X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$; then Y^1 is $C(R^{1m2})$ or N; Y^2 is $C(R^{2m2})$ or N; Y^3 is $C(R^{3m2})$ or N; Y^4 is $C(R^{4m2})$ or N; and Y^5 is $C(R^{5m2})$ or N; wherein

R^{1m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1m2} combines with R^{2m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2m2} combines with R^{3m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3m2} combines with R^{4m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4m2} combines with R^{5m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{3m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN.

[0246] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount

of a compound of Formula (V), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; or

X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l};

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^{1a} and $R^{1a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ are each H; orR^{2a} and $R^{2a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H; or

R^{1a} and R^{3a} combine to form a cycloalkyl ring, wherein the cycloalkyl ring may be unsubstituted or substituted with one or more C_{1-6} alkyl, and $R^{1a'}$, R^{2a}, $R^{2a'}$, and $R^{3a'}$ are each independently selected from the group consisting of H and C_{1-6} alkyl;R^{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3b} and $R^{3b'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$;

wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{2e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{3e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{4e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{5e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2; or

R^{1e2} combines with R^{2e2} to form a heteroaryl ring, and R^{3e2}, R^{4e2}, and R^{5e2} are each H;

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l}; then Y^1 is $C(R^{1l2})$; Y^2 is $C(R^{2l2})$; Y^3 is $C(R^{3l2})$; Y^4 is $C(R^{4l2})$; and Y^5 is $C(R^{5l2})$; wherein

R^{1l2} is H, C_{1-6} haloalkyl, or NO_2;

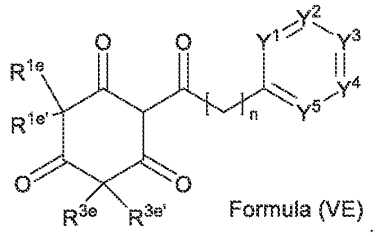
R^{2l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5l2} is H, C_{1-6} haloalkyl, or NO_2.

[0247] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:



Formula (VE)

[0248] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein n is 0.

[0249] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein Y^1 is $C(NO_2)$.

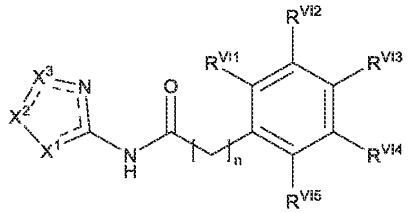
[0250] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein Y^3 is $C(CF_3)$.

[0251] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3.

[0252] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, or R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each CH_3.

[0253] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formulae (V) or (VE), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{1b} is cycloalkyl or heteroaryl.

[0254] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI):



Formula (VI)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

X^1 is NR^1, X^2 is CR^2, and X^3 is N or CH;

X^1 is O, X^2 is CR^2, and X^3 is N;

X^1 is N, X^2 is NR^1, and X^3 is N; or

X^1 is NR^3, X^2 is N, and X^3 is N;

n is 0 or 1;

R^1 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^1 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^2 is selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, SO_2-C_{1-6} alkyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

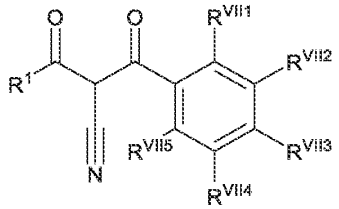
R^{VI1}, R^{VI2}, R^{VI3}, R^{VI4}, and R^{VI5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

[0255] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^3 is C_{4-6} alkyl or phenyl substituted with one or more halo.

[0256] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{VI1} is H or NO_2. In some embodiments, R^{VI1} is H. In some embodiments, R^{VI1} is NO_2.

[0257] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{VI3} is H or CF_3. In some embodiments, R^{VI3} is H. In some embodiments, R^{VI3} is CF_3.

[0258] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

R^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, and C_1 alkyl-heteroaryl;

wherein the C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, or C_1 alkyl-heteroaryl of R^1 is unsubstituted or substituted with halo;

R^{VII1}, R^{VII2}, R^{VII3}, R^{VII4}, and R^{VII5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

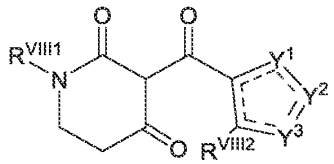
[0259] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^1 is aryl or C_1 alkyl-aryl, wherein the aryl or C_1 alkyl-aryl may be unsubstituted or substituted with one or more halo.

[0260] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{VII1} is H or NO_2. In some embodiments, R^{VII1} is H. In some embodiments, R^{VII1} is NO_2.

[0261] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{VII2} is H, halo, or SO_2-C_{1-6} alkyl. In some embodiments, R^{VII2} is H. In some embodiments, R^{VII2} is halo. In some embodiments, R^{VII2} is SO_2-C_{1-6} alkyl.

[0262] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^{VII3} is H or CF_3. In some embodiments, R^{VII3} is H. In some embodiments, R^{VII3} is CF_3.

[0263] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII):



Formula (VIII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

Y^1 is CR^1, Y^2 is N, and Y^3 is NR^3;

Y^1 is CR^1, Y^2 is O or S, and Y^3 is CR^3;

Y^1 is N, Y^2 is CR^2, and Y^3 is O or S; or

Y^1 is O or S, Y^2 is CR^2, and Y^3 is CR^3;

R^1 and R^2 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^1 or R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^3 combines with R^{VIII2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{VIII1} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{VIII1} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{VIII2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

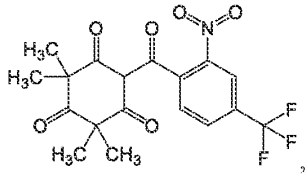
R^{VIII2} combines with R^3 to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl.

[0264] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^1 is H or CF_3. In some embodiments, R^1 is H. In some embodiments, R^1 is CF_3.

[0265] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^2 is H or CF_3. In some embodiments, R^2 is H. In some embodiments, R^2 is CF_3.

[0266] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII), or the pharmaceutically acceptable salts or tautomers thereof, wherein R^3 is H or C_{1-6} alkyl. In some embodiments, R^3 is H. In some embodiments, R^3 is C_{1-6} alkyl.

[0267] The present disclosure also provides compounds of Formulae (V), (VE), (VI), (VII), and (VIII), as described herein

[0268] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound, wherein the compound is , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0269] In some embodiments, the disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0270] In some embodiments, the disclosure provides a use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-

O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0271] In some embodiments, the disclosure provides a use of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising administering to the subject an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0272] In some embodiments, the disclosure provides a use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and the compound is of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0273] In some embodiments, the disclosure provides a use of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of

HPD in a human subject in need thereof, wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0274] In some embodiments, the disclosure provides a compound for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject, wherein the compound is of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0275] In some embodiments, the disclosure provides a compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject.

[0276] In some embodiments, the disclosure provides a pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein the method comprises administering the pharmaceutical formulation to a subject having the condition, and the compound is any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE),

(VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0277] In some embodiments, the disclosure provides a pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein the method comprises administering the pharmaceutical formulation to a subject having the condition.

[0278] In some embodiments, the disclosure provides a medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the treatment comprises administering the medicament to a subject having the condition, and the compound is of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0279] In some embodiments, the disclosure provides a medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of the compound of any one of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), and (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof,

wherein the treatment comprises administering the medicament to a subject having the condition.

[0280] In some embodiments, administration of a compound of the disclosure inhibits SPR less than nitisinone. In some embodiments, the compound has inhibitory activity for SPR that is at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% less than nitisinone. Inhibitory activity for HPD and for SPR can be measured by any known means, for example, *in vitro* biochemical assays and *in vivo* cell-base characterization assays such as those described in Biological Examples 3, 5, and 6.

[0281] The term "inhibitor," as used herein, refers to a molecule such as a compound, a drug, enzyme, or a hormone that blocks or otherwise interferes with a particular biologic activity. For example, "HPD inhibitor," as used herein, refers to a molecule that interferes with HPD. Interference of an inhibitor for with a particular biologic activity can be measured by any known means, for example, *in vitro* biochemical assays and *in vivo* cell-base characterization assays such as those described in Biological Examples 3, 5, and 6.

[0282] In some embodiments, a compound of the disclosure is a selective HPD inhibitor. The term "selective inhibitor," as used herein, refers to an inhibitor that specifically targets and inhibits the activity of a particular biological molecule, pathway, or process while exhibiting minimal or no effect inhibition on other molecules or pathways. Selective inhibitors may modulate specific cellular functions or biochemical reactions associated with the target without causing significant off-target effects. A selective inhibitor may have an IC_{50} value for the target that is lower than an IC_{50} value for other off-target molecules. For example, "selective HPD inhibitor," as used herein, refers to a molecule that interferes with HPD with no or minimal off-target activity on other molecules (*e.g.*, SPR, enzymes in the tyrosine catabolism pathway, enzymes homologous to HPD, etc.) Comparative inhibitory activity for particular biologic activity compared with off-target molecules can be measured by any known means, for example, *in vitro* biochemical assays and *in vivo* cell-base characterization assays such as those described in Biological Examples 3, 5, and 6.

[0283] The term "IC_{50}," as used herein, refers to concentrations at which a measurable activity, phenotype or response, for example growth or proliferation of cells such as tumor cells, is inhibited by 50%. IC_{50} values can be estimated from an appropriate dose-response curve, for example, by eye or by using appropriate curve fitting or statistical software. More accurately, IC_{50} values may be determined using non-linear regression analysis. IC_{50} values can be

measured by any known means, for example, *in vitro* biochemical assays and *in vivo* cell-base characterization assays such as those described in Biological Examples 3, 5, and 6.

[0284] In some embodiments, a compound of the disclosure inhibits HPD more than SPR. Inhibitory activity for HPD and for SPR can be measured by any known means, for example, *in vitro* biochemical assays and *in vivo* cell-base characterization assays such as those described in Biological Examples 3, 5, and 6. In some embodiments the IC_{50} of the compound for HPD is less than the IC_{50} for SPR. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 500, at least 1000, at least 10000 or at least 100000. The SPR:HPD IC_{50} ratio of the compound may be referred to as the "selectivity" of the compound for SPR and HPD.

[0285] In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 1. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 2. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 5. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 10. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 30. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 30. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 40. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 50. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 60. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 70. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 80. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 90. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 100. In

some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 500. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 1000. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 10000. In some embodiments, the SPR:HPD IC_{50} ratio of the compound is at least 100000.

[0286] In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 600 nM, greater than 650 nM, greater than 700 nM, greater than 750 nM, greater than 800 nM, greater than 850 nM, greater than 900 nM, greater than 950 nM, greater than 1000 nM, greater than 1050 nM, greater than 1100 nM, greater than 1150 nM, greater than 1200 nM, greater than 1250 nM, greater than 1300 nM, greater than 1350 nM, greater than 1400 nM, greater than 1450 nM, greater than 1500 nM, greater than 1550 nM, greater than 1600 nM, greater than 1650 nM, greater than 1700 nM, greater than 1750 nM, greater than 1800 nM, greater than 1850 nM, greater than 1900 nM, greater than 1950 nM, greater than 2000 nM, greater than 2050 nM, greater than 2100 nM, greater than 2150 nM, greater than 2200 nM, greater than 2250 nM, greater than 2300 nM, greater than 2350 nM, greater than 2400 nM, greater than 2450 nM, greater than 2500 nM, greater than 2550 nM, greater than 2600 nM, greater than 2650 nM, greater than 2700 nM, greater than 2750 nM, greater than 2800 nM, greater than 2850 nM, greater than 2900 nM, greater than 2950 nM, greater than 3000 nM n, greater than 5000 nM, greater than 10000 nM, greater than 100 μM, greater than 500 μM, greater than 1 mM, greater than 10 mM, or greater than 100 mM.

[0287] In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 600 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 700 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 800 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 900 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1000 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1100 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1200 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1300 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1400 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1500 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1600 nM. In some

embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1700 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1800 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1900 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2000 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2100 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2200 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2300 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2400 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2500 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2600 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2700 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2800 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 2900 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 3000 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 5000 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 10000 nM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 100 μM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 500 μM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 1 mM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 10 mM. In some embodiments, a compound of the disclosure inhibits SPR with an *in vitro* IC_{50} greater than 100 mM.

[0288] In some embodiments, a compound of the disclosure inhibits HPD more than nitisinone. For example, in some embodiments, the IC_{50} of the compound for HPD ($HPD_{compound}$ IC_{50}) is less than the IC_{50} of nitisinone for HPD ($HPD_{nitisinone}$ IC_{50}). In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least

32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 500, at least 1000, at least 10000 or at least 100000.

[0289] In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 1. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 2. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 5. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 10. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 30. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 30. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 40. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 50. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 60. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 70. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 80. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 90. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 100. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 500. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 1000. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 10000. In some embodiments, the $HPD_{nitisinone}$: $HPD_{compound}$ IC_{50} ratio is at least 100000.

[0290] In some embodiments, a compound of the disclosure inhibits SPR less than nitisinone. For example, in some embodiments, the IC_{50} of the compound for SPR ($SPR_{compound}$ IC_{50}) is greater than the IC_{50} of nitisinone for SPR ($SPR_{nitisinone}$ IC_{50}). In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at

least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, at least 50, at least 51, at least 52, at least 53, at least 54, at least 55, at least 56, at least 57, at least 58, at least 59, at least 60, at least 61, at least 62, at least 63, at least 64, at least 65, at least 66, at least 67, at least 68, at least 69, at least 70, at least 71, at least 72, at least 73, at least 74, at least 75, at least 76, at least 77, at least 78, at least 79, at least 80, at least 81, at least 82, at least 83, at least 84, at least 85, at least 86, at least 87, at least 88, at least 89, at least 90, at least 91, at least 92, at least 93, at least 94, at least 95, at least 96, at least 97, at least 98, at least 99, at least 100, at least 500, at least 1000, at least 10000 or at least 100000.

[0291] In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 1. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 2. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 5. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 10. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 30. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 30. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 40. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 50. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 60. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 70. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 80. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 90. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 100. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 500. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 1000. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 10000. In some embodiments, the $SPR_{compound}$:$SPR_{nitisinone}$ IC_{50} ratio is at least 100000.

[0292] In some embodiments, disclosed herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound is a selective HPD inhibitor.

[0293] In some embodiments, disclosed herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound inhibits HPD in the subject, wherein the compound results in a lower inhibition of SPR than HPD.

[0294] In some embodiments, disclosed herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound inhibits HPD in the subject, wherein the compound results in a lower inhibition of SPR than in a subject treated with nitisinone.

[0295] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound does not inhibit SPR.

[0296] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound results in a lower inhibition of SPR than HPD.

[0297] In some embodiments, administration of a compound of the disclosure to a subject lowers dihydrobiopterin (BH2) levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 2-fold, a 3-fold, a 4-fold, a 5-fold, a 6-fold, a 7-fold, an 8-fold, a 9-fold, a 10-fold, an 11-fold, a 12-fold, a 13-fold, a 14-fold, a 15-fold, a 16-fold, a 17-fold, an 18-fold, a 19-fold, a 20-fold, a 21-fold, a 22-fold, a 23-fold, a 24-fold, a 25-fold, a 26-fold, a 27-fold, a 28-fold, a 29-fold, a 30-fold, a 40-fold, a 50-fold, a 60-fold, a 70-fold, a 80-fold, a 90-fold, a 100-fold, a 500-fold, a 1000-fold, a 5000-fold, or a 10000-foldlower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 2-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 3-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 4-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 5-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 6-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments,

administration of a compound of the disclosure to a subject results in a 7-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in an 8-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 9-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 10-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 15-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 20-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 25-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 30-fold lower reduction of BH2 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject does not result in BH2 deficiency in the subject.

In some embodiments, administration of a compound of the disclosure to a subject results in a lower reduction of tetrahydrobiopterin (BH4) levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 2-fold, a 3-fold, a 4-fold, a 5-fold, a 6-fold, a 7-fold, an 8-fold, a 9-fold, a 10-fold, an 11-fold, a 12-fold, a 13-fold, a 14-fold, a 15-fold, a 16-fold, a 17-fold, an 18-fold, a 19-fold, a 20-fold, a 21-fold, a 22-fold, a 23-fold, a 24-fold, a 25-fold, a 26-fold, a 27-fold, a 28-fold, a 29-fold, a 30-fold, a 40-fold, a 50-fold, a 60-fold, a 70-fold, an 80-fold, a 90-fold, a 100-fold, a 500-fold, a 1000-fold, a 5000-fold, or a 10000-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 2-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 3-fold lower reduction of BH levels in the subject compared to a comparable subject

treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 4-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 5-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 6-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 7-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in an 8-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 9-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 10-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 15-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 20-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 25-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject results in a 30-fold lower reduction of BH4 levels in the subject compared to a comparable subject treated with nitisinone. In some embodiments, administration of a compound of the disclosure to a subject does not result in BH4 deficiency in the subject.

[0298] BH2 and BH4 levels in a subject may be measured by any known means, for example derivatization with benzoyl chloride coupled with liquid chromatography-tandem mass spectrometry analysis (see, for example, Yuan TF et al, A novel and reliable method for tetrahydrobiopterin quantification: Benzoyl chloride derivatization coupled with liquid chromatography-tandem mass spectrometry analysis. Free Radic Biol Med. 2018 Apr;118:119-125, which is hereby incorporated by reference in its entirety.) BH2 and BH4 levels can also be

determined by indirect chemical oxidation using iodine oxidation treatment and two corresponding liquid chromatography fluorometric runs (see, for example, T. Fukushima, J.C. Nixon, Analysis of reduced forms of biopterin in biological tis- sues and fluids, Anal. Biochem. 102 (1980) 176–188), which is hereby incorporated by reference in its entirety.)

[0299] In some embodiments, disclosed herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound inhibits HPD in the subject, wherein the administering results in a lower reduction in BH4 levels in the subject compared to a subject treated with nitisinone.

[0300] In some embodiments, disclosed herein is a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound inhibits HPD in the subject, wherein the administering results in a lower reduction in BH2 levels in the subject compared to a subject treated with nitisinone.

[0301] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound results in a lower reduction in BH4 levels in the subject compared to a subject treated with nitisinone.

[0302] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the compound results in a lower reduction in BH2 levels in the subject compared to a subject treated with nitisinone.

[0303] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the treatment provides improved neurocognitive function in the subject compared to a subject treated with nitisinone.

[0304] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure to replace nitisinone, or other non-selective HPD inhibitors, wherein the subject has neurocognitive symptoms, wherein the method stabilizes neurocognitive function.

[0305] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure to replace nitisinone, or other non-selective HPD inhibitors, wherein the subject is having neurocognitive decline, wherein the method stabilizes neurocognitive function.

[0306] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure to replace nitisinone, or other non-selective HPD inhibitors, wherein the subject has neurocognitive symptoms, wherein the method improves neurocognitive function.

[0307] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure to replace nitisinone, or other non-selective HPD inhibitors, wherein the subject has neurocognitive decline, wherein the method improves neurocognitive function.

[0308] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the subject is currently taking a non-selective HPD inhibitor, such as nitisinone, and wherein the subject stops taking the non-selective HPD inhibitor.

[0309] In some embodiments, disclosed herein is a method of inhibiting HPD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure, wherein the subject has taken a non-selective HPD inhibitor, such as nitisinone.

[0310] As described herein, the compounds may be used to treat a condition in a subject. In some embodiments, the condition is an inborn error of metabolism, myalgic encephalomyelitis (also known as chronic fatigue syndrome), Parkinson's disease, Lewy Body dementia, mood disorders, autoimmune disorders, inflammatory disorders, neuropathic pain, refractory hypertension, low sex drive, attention-deficit/hyperactivity disorder (ADHD), sleep disorders, restless leg syndrome, obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), substance abuse disorder, chronic constipation, tremor disorders, CoQ10 deficiency, and oculocutaneous albinism. In some embodiments, the condition is an inborn error

of metabolism. In some embodiments, the condition is Parkinson's disease. In some embodiments, the condition is Lewy Body dementia. In some embodiments, the condition is an autoimmune disorder. In some embodiments, the condition is an inflammatory disorder. In some embodiments, the condition is neuropathic pain. In some embodiments, the condition is refractory hypertension. In some embodiments, the condition is low sex drive. In some embodiments, the condition is attention-deficit/hyperactivity disorders (ADHD). In some embodiments, the condition is sleep disorders. In some embodiments, the condition is restless leg syndrome. In some embodiments, the condition is obsessive-compulsive disorder (OCD). In some embodiments, the condition is panic disorders. In some embodiments, the condition is post-traumatic stress disorder (PTSD). In some embodiments, the condition is substance abuse disorder. In some embodiments, the condition is chronic constipation. In some embodiments, the condition is a tremor disorder. In some embodiments, the condition is CoQ10 deficiency. In some embodiments, the condition is oculocutaneous albinism.

[0311] In some embodiments, the condition is a mood disorder. In some embodiments, the mood disorder is depression.

[0312] In some embodiments, the inborn error of metabolism is an inborn error of tyrosine metabolism. In some embodiments, the inborn error of tyrosine metabolism is tyrosinemia type I, tyrosinemia type II, tyrosinemia type III, alkaptonuria, or hawkinsinuria. In some embodiments, the condition is tyrosinemia type I. In some embodiments, the condition is tyrosinemia type II. In some embodiments, the condition is tyrosinemia type III. In some embodiments, the condition is alkaptonuria. In some embodiments, the condition is hawkinsinuria. In some embodiments, an inborn error of metabolism can comprise an inborn error of phenylalanine metabolism. In some embodiments, the condition is phenylketonuria.

[0313] In some embodiments, the methods increase overall survival of a subject. In some embodiments, the methods increase overall survival of a subject by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%. In some embodiments, the methods increase overall survival of a subject by at least about 10%. In some embodiments, the methods increase overall survival of a subject by at least about 20%. In some embodiments, the methods increase overall survival of a subject by at least about 10%.

[0314] In some embodiments, the methods further comprise utilizing metabolites to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing phenylalanine levels to direct therapy (*e.g.*, with respect to increasing/decreasing dose amounts or dose frequency in a subject.) In some embodiments, methods of the disclosure can further comprise utilizing tyrosine levels to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing BH4 levels to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing BH2 levels to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing metabolites to monitor subject response. In some embodiments, methods of the disclosure can further comprise utilizing metabolites to titrate dosing. In some embodiments, methods of the disclosure can further comprise utilizing sepiapterin levels to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing biopterin levels to direct therapy. In some embodiments, methods of the disclosure can further comprise utilizing succinylacetone levels to direct therapy.

[0315] In some embodiments, the compositions and the methods further comprise administering BH4, BH2, levodopa, carbidopa and/or serotonin supplementation.

[0316] In some embodiments, the compositions and methods of the disclosure comprise administering BH4 and/or BH2 in combination with an HPD inhibitor for treating a condition.

[0317] In some embodiments, the compositions and methods of the disclosure comprise administering sepiapterin in combination with an HPD inhibitor for treating a condition.

[0318] In some embodiments, the compositions and methods of the disclosure comprise administering BH4 and/or BH2 in combination with nitisinone for the treatment of an inborn error of metabolism. In some embodiments, the compositions and methods of the disclosure comprise administering BH4 and BH2 supplementation in combination with nitisinone for the treatment of tyrosinemia type I. In some embodiments, the compositions and methods of the disclosure comprise administering BH4 and BH2 supplementation in combination with nitisinone for the treatment of alkaptonuria. In some embodiments, the compositions and methods of the disclosure comprise administering BH4 and BH2 supplementation in combination with nitisinone for the treatment of hawkinsinuria.

[0319] In some embodiments, the compositions and methods of the disclosure comprise administering a dopamine precursor therapy in combination with an HPD inhibitor for treating a condition.

[0320] In some embodiments, the compositions and methods of the disclosure comprise administering a dopamine precursor therapy in combination with nitisinone for the treatment of an inborn error of metabolism.

[0321] In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa in combination with an HPD inhibitor for treating a condition.

[0322] In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa and serotonin supplementation in combination with an HPD inhibitor for treating a condition.

[0323] In some embodiments, the compositions and methods of the disclosure comprise administering serotonin supplementation in combination with an HPD inhibitor for treating a condition.

[0324] In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa in combination with nitisinone for the treatment of inborn errors of metabolism. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa in combination with nitisinone for the treatment of tyrosinemia type I. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa in combination with nitisinone for the treatment of alkaptonuria. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa in combination with nitisinone for the treatment of hawkinsinuria.

[0325] In some embodiments, the compositions and methods of the disclosure comprise administering serotonin supplementation in combination with nitisinone for the treatment of inborn errors of metabolism. In some embodiments, the compositions and methods of the disclosure comprise administering serotonin supplementation in combination with nitisinone for the treatment of tyrosinemia type I. In some embodiments, the compositions and methods of the disclosure comprise administering serotonin supplementation in combination with nitisinone for the treatment of alkaptonuria. In some embodiments, the compositions and methods of the disclosure comprise administering serotonin supplementation in combination with nitisinone for the treatment of hawkinsinuria.

[0326] In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa and serotonin supplementation in combination with nitisinone for the treatment of inborn errors of metabolism. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa and serotonin supplementation in combination with nitisinone for the treatment of tyrosinemia type I. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa and serotonin supplementation in combination with nitisinone for the treatment of alkaptonuria. In some embodiments, the compositions and methods of the disclosure comprise administering levodopa and/or an inhibitor of peripheral DOPA decarboxylase such as carbidopa and serotonin supplementation in combination with nitisinone for the treatment of hawkinsinuria.

[0327] The terms "effective amount" or "therapeutically effective amount," when used in connection with a compound, refer to a sufficient amount of the compound to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic use is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using routine experimentation. Thus, the expression "effective amount" generally refers to the quantity for which the active substance has therapeutic effects. In the present disclosure the active substance is an inhibitor of HPD.

[0328] The term "disorder," as used herein, refers to and is used interchangeably with the terms disease, condition, or illness, unless otherwise indicated.

Amino acid (AA) modulation therapy

[0329] In some embodiments, compositions and the methods further comprise administering an AA modulation therapy to lower an average plasma level of an amino acid in a subject. In some embodiments, compositions of the disclosure are administered to a subject in combination with an AA modulation therapy that delivers less than a recommended dietary requirement of one or more amino acids (*e.g.*, tyrosine, phenylalanine, or both) to a subject. In some embodiments, the AA modulation therapy comprises a diet (*e.g.*, a food-based diet.) In some

embodiments, the AA modulation therapy comprises a dietary product (*e.g.*, a plurality of amino acids, such as in powder form.) In some embodiments, the AA modulation therapy comprises a diet (*e.g.*, a food-based diet) and a dietary product (*e.g.*, a plurality of amino acids, such as in powder form.)

[0330] Daily recommended dietary requirement, as used herein, refers to the daily dietary intake level (*e.g.*, of protein, carbohydrates, fat, and amino acids) that suffices to meet the nutrient requirements (*e.g.*, protein, carbohydrate, fat, and amino acid requirements) of nearly all (*e.g.*, 95% or more) healthy person of a specific sex and age. For example, recommended dietary intake levels may be recommended dietary allowance (RDA) as determined by the Food and Nutrition Board of the Institute of Medicine. Also for example, recommended dietary intake levels may be daily median intake as recommended by the National Health and Nutrition Examination Survey (NHANES).

[0331] Average plasma levels of a biomarker (*e.g.*, an amino acid level, such as a tyrosine level or a phenylalanine level), as used herein, refers to levels of a biomarker (*e.g.*, an amino acid) as measured from a blood panel. For example, in some embodiments, blood is collected for amino acid panel(s) approximately 2 hours (+/- 60 min) after a meal. Also for example, in some embodiments, for baseline average plasma levels of a biomarker (*e.g.*, of an amino acid such as tyrosine or phenylalanine), two blood collections on different days occur before treatment (*e.g.*, during screening.) In some embodiments, average plasma levels of a biomarker (*e.g.*, of an amino acid such as tyrosine or phenylalanine) after treatment with an AA modulation therapy involve blood collection 1-5 days (*i.e.*, 1, 2, 3, 4, or 5 days) after treatment with AA modulation therapy.

[0332] In some embodiments, the AA modulation therapy decreases an amino acid level in a subject. In some embodiments, the amino acid level is decreased by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90%. In some embodiments, the amino acid level is decreased by at least about 10%. In some embodiments, the amino acid level is decreased by at least about 20%. In some embodiments, the amino acid level is decreased by at least about 50%.

[0333] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%,

less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of a recommended dietary requirement of tyrosine for the subject's age group, as determined by the Food and Nutrition Board of the Institute of Medicine.

[0334] Recommended dietary requirements may vary based on factors including subjects age, sex, and physical activity. For example, recommended dietary requirements for tyrosine may vary as shown:

	Tyrosine (mg/kg/day)
Infants (0.3 to 1 year)	29.9
Children (1 to 3 years)	29.3
Adult – low physical activity	26.6
Adult – moderate physical activity	34.6
Adult – intense physical activity	42.6

These reference values are adapted from: Wu G. Dietary protein intake and human health. Food & Function. 2016;7(3):1251-1265. doi:10.1039/c5fo01530h, which is hereby incorporated by reference in its entirety. Also for example, recommended dietary requirements for combined intake of phenylalanine and tyrosine may vary as shown:

	Phenylalanine + Tyrosine (mg/kg/day)
Infants (0-6 months)	135
Infants (6-12 months)	84
Children (1-3 years)	54
Children (4-8 years)	41
Children (9-13 years)	41 (boys), 38 (girls)
Adolescents (14-18)	38 (boys), 35 (girls)
Adults	33

These reference values are adapted from: Institute of Medicine. 2006. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: The National Academies Press. https://doi.org/10.17226/11537, which is hereby incorporated by reference in its entirety.

[0335] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of a recommended dietary allowance (RDA) of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0336] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of an RDA of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0337] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of an RDA of tyrosine and phenylalanine combined, for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine. In some embodiments, the recommended dietary allowance of tyrosine and phenylalanine is 33 mg/kg/day.

[0338] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of average recommended dietary intake of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine. In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of average recommended dietary intake of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0339] In some embodiments, the AA modulation therapy provides less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% average recommended dietary intake of each of tyrosine and phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0340] In some embodiments, the AA modulation therapy provides less than the daily median intake of tyrosine. In some embodiments, the AA modulation therapy provides less than 50%,

less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of the daily median intake amount of tyrosine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the daily median intake of tyrosine is 3.9 g/day.

[0341] In some embodiments, the AA modulation therapy provides less than the daily median intake of phenylalanine. In some embodiments, a dietary product provides less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, less than 1%, less than 0.5%, or less than 0.1% of the daily median intake amount of phenylalanine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the median intake of phenylalanine is 4.8 g/day.

[0342] In some embodiments, the AA modulation therapy comprises a diet (*e.g.*, a food-based diet) that has less than a recommended dietary requirement of one or more amino acids. In some embodiments, the diet is devoid of one or more amino acid. In some embodiments, after detecting an absence or a decreased level of a biomarker of an amino acid metabolism pathway in a subject, the subject is administered an AA modulation therapy that removes the amino acid from the subject's diet. In some embodiments, the diet is administered via tube feeding.

[0343] "Devoid of", as used herein, is used interchangeably with "does not comprise" or "lacks".

[0344] Diet, as used herein, refers to the nutritional intake consumed by the subject from meals, snacks, and drinks throughout the day. For example, the diet may be a food-based diet that comprises the subject's food and beverages over the course of a day. The diet may also comprise meal replacement products, medical food, or parenteral nutritional intake.

[0345] In some embodiments, the diet accounts for almost all food consumed by the subject. For example, in some embodiments, the diet accounts for at least 80%, at least 90%, at least 95%, or at least 95% of calories from food consumed by the subject. In some embodiments, the diet accounts for all food consumed by the subject. For example, in some embodiments, the diet accounts for 100% of calories from food consumed by the subject.

[0346] In some embodiments, the diet is a low-protein diet. In some embodiments, the low-protein diet comprises less than about 2 g/day, about 1.75 g/day, about 1.5 g/day, about 1.25 g/day, about 1 g/day, about 0.75 g/day, or about 0.5 g/day of protein. In some embodiments, a composition of the disclosure is administered to a subject that is on a low-protein diet comprising less than about 500 mg/day, about 450 mg/day, about 400 mg/day, about 350

mg/day, about 300 mg/day, about 250 mg/day, about 200 mg/day, about 150 mg/day, about 100 mg/day, or about 50 mg/day of protein.

[0347] In some embodiments, the diet comprises meals with modified types of proteins, amino acids, or peptides that contain low levels of specific amino acids. In some embodiments, the diet comprises meals with modified levels of one amino acid. In some embodiments, the amino acid is tyrosine. In some embodiments, the amino acid is phenylalanine. In some embodiments, two amino acid levels are lowered in a subject by administering to the subject meals with modified levels of the amino acids or by modifying amino acid levels for the subject's daily food intake. In some embodiments, the two amino acids are tyrosine and phenylalanine.

[0348] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a recommended dietary requirement of tyrosine for the subject's age group, as determined by the Food and Nutrition Board of the Institute of Medicine.

[0349] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a recommended dietary allowance (RDA) of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0350] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of the daily median intake amount of tyrosine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the daily median intake of tyrosine is 3.9 g/day.

[0351] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than

about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an RDA of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0352] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0353] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of the daily median intake amount of phenylalanine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the median intake of phenylalanine is 4.8 g/day.

[0354] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an average recommended dietary intake of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine and less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of average recommended dietary intake of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0355] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than

about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an average recommended dietary intake of each of tyrosine and phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0356] In some embodiments, the diet comprises less than about 75%, less than about 70%, less than about 65%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a combined RDA of tyrosine and phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine. In some embodiments, the combined RDA of tyrosine and phenylalanine is 33 mg/kg/day.

Dietary Product

[0357] In some embodiments, the AA modulation therapy comprises a dietary product. In some embodiments, treatments comprise administering to a subject a therapeutically effective amount of an inhibitor of HPD and a dietary product, wherein the dietary product comprises less than a recommended dietary requirement of one or more amino acids (*e.g.*, tyrosine, phenylalanine, or tyrosine and phenylalanine.) In some embodiments, the dietary product is administered with food (*e.g.*, with food from a low-protein food-based diet.) In some embodiments, the dietary product is a sole source of protein for the subject. In some embodiments, the dietary product is a sole source of amino acids for the subject. In some embodiments, the dietary product is a sole source of calories for the subject.

[0358] In some embodiments, the dietary product provides at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% of the amino acids consumed by the subject. In some embodiments, the dietary product provides about 100% of the amino acids consumed by the subject. In some embodiments, the dietary product is substantially a sole source of protein for the subject. In some embodiments, the dietary product is substantially a sole source of amino acids for the subject. In some embodiments, the dietary product is substantially a sole source of calories for the subject.

[0359] The term "source", such as in the phrase "substantially a sole source," as used herein, refers to a provider of nutrition such as a diet, a dietary regimen, or a dietary product as used herein. The phrase "substantially a sole source," as used herein, refers to said source providing almost all if not all of the indicated nutritional component. For example, the phrase "a dietary regimen is substantially a sole source of calories for a subject" indicates the dietary regimen provides almost all, if not all calories (including calories from carbohydrates, protein, and fat) taken in by a subject. Also for example, the phrase "a dietary regimen is substantially a sole source of amino acids for a subject" indicates the dietary regimen provides almost all, if not all of the amino acids taken in by a subject. For example, substantially a sole source may refer to at least 90% of the stated daily intake of the nutritional item originating from the stated source.

[0360] In some embodiments, the dietary product accounts for almost all calories consumed by the subject (*e.g.*, in some embodiments, the AA modulation therapy consists of a dietary product without a food-based diet.) For example, in some embodiments, the dietary product account for at least 80%, at least 90%, at least 95%, or at least 95% of calories consumed by the subject. In some embodiments, the dietary accounts all calories consumed by the subject. For example, in some embodiments, the diet accounts for 100% of calories consumed by the subject.

[0361] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a recommended dietary requirement of tyrosine for the subject's age group, as determined by the Food and Nutrition Board of the Institute of Medicine.

[0362] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a recommended dietary allowance (RDA) of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0363] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of the daily median intake amount of

tyrosine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the daily median intake of tyrosine is 3.9 g/day.

[0364] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an RDA of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0365] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0366] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of the daily median intake amount of phenylalanine as determined by the National Health and Nutrition Examination Survey (NHANES). In some embodiments, the median intake of phenylalanine is 4.8 g/day.

[0367] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an average recommended dietary intake of tyrosine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine and less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of average recommended dietary intake of phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0368] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of an average recommended dietary

intake of each of tyrosine and phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine.

[0369] In some embodiments, the dietary product comprises less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 1%, less than about 0.5%, or less than about 0.1% of a combined RDA of tyrosine and phenylalanine for the subject's age group as determined by the Food and Nutrition Board of the Institute of Medicine. In some embodiments, the combined RDA of tyrosine and phenylalanine is 33 mg/kg/day.

[0370] In some embodiments, the dietary product is devoid of at least 1, 2, 3, 4, 5, 6, 7, or 8 amino acids. In some embodiments, the dietary product is devoid of at least 1 amino acid. In some embodiments, the dietary product is devoid of at least 2 amino acids. In some embodiments, the dietary product is devoid of at least 3 amino acids. In some embodiments, the dietary product is devoid of at least 4 amino acids. In some embodiments, the dietary product is devoid of at least 5 amino acids.

[0371] In some embodiments, the dietary product is devoid of at least tyrosine. In some embodiments, the dietary product is devoid of at least phenylalanine. In some embodiments, the dietary product is devoid of tyrosine and phenylalanine.

[0372] In some embodiments, the dietary product is devoid of tyrosine and contains less than about 100 mg/kg/day, about 95 mg/kg/day, about 90 mg/kg/day, about 85 mg/kg/day, about 80 mg/kg/day, about 75 mg/kg/day, about 70 mg/kg/day, about 65 mg/kg/day, about 60 mg/kg/day, about 55 mg/kg/day, about 50 mg/kg/day, about 45 mg/kg/day, about 40 mg/kg/day, about 35 mg/kg/day, about 30 mg/kg/day, about 25 mg/kg/day, about 20 mg/kg/day, about 15 mg/kg/day, about 10 mg/kg/day, or about 5 mg/kg/day of phenylalanine. In some embodiments, the dietary product is devoid of tyrosine and contain less than about 30 mg/kg/day of phenylalanine. In some embodiments, the dietary product is devoid of at least tyrosine and contain less than about 25 mg/kg/day of phenylalanine. In some embodiments, the dietary product is devoid of at least tyrosine and contain less than about 20 mg/kg/day of phenylalanine. In some embodiments, the dietary product is devoid of at least tyrosine and contain less than about 15 mg/kg/day of phenylalanine.

[0373] The dietary product comprises at least ten amino acids or salts thereof. In some embodiments, the dietary product comprises 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 amino acids

or a salt thereof. In some embodiments, the dietary product comprises 10 amino acids or a salt thereof. In some embodiments, the dietary product comprises 14 amino acids or a salt thereof. In some embodiments, the dietary product comprises 18 amino acids or a salt thereof.

[0374] In some embodiments, the dietary product comprises 1, 2, 3, 4, 5, 6, 7, 8, or 9 essential amino acids or salts thereof. In some embodiments, the dietary product comprises 7, 8, or 9 essential amino acids or salts thereof. In some embodiments, the dietary product comprises 8 essential amino acids or salts thereof. In some embodiments, the dietary product comprises 9 essential amino acids or salts thereof.

[0375] Essential amino acids, as used herein, refers to histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine .

[0376] In some embodiments, the dietary product comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 7, 8, 9, 10, or 11 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 7 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 8 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 9 non-essential amino acids or salts thereof.

[0377] Non-essential amino acids, as used herein, refers to alanine, asparagine, aspartic acid, glutamic acid, arginine, cysteine, glutamine, tyrosine, glycine, proline, and serine. Some non-essential amino acids are conditionally essential amino acids. Conditionally essential amino acids, as used herein, refers to asparagine, arginine, cysteine, glutamine, tyrosine, glycine, proline, and serine.

[0378] In some embodiments, the dietary product comprises essential amino acids or salts thereof and non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 1, 2, 3, 4, 5, 6, 7, 8, or 9 essential amino acids or salts thereof and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 7, 8, or 9 essential amino acids or salts thereof and 6, 7, 8, or 9 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 8 or 9 essential amino acids or salts thereof and 8 or 9 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 9 essential amino acids or salts thereof and 7 non-essential amino acids or salts thereof. In some embodiments, the dietary product comprises 9 essential amino acids or salts thereof and 8 non-essential amino acids or salts thereof. In some

embodiments, the dietary product comprises 9 essential amino acids or salts thereof and 9 non-essential amino acids or salts thereof.

[0379] In some embodiments, the dietary product comprises histidine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, arginine, glutamine, alanine, aspartic acid, asparagine, glutamic acid or proline. In some embodiments, the dietary product comprises L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-cysteine, L-phenylalanine, L-tyrosine, L-threonine, L-tryptophan, L-valine, L-arginine, L-glutamine, L-alanine, L-aspartic acid, L-asparagine, L-glutamic acid, or L-proline.

[0380] In some embodiments, a composition comprises histidine or a salt thereof, such as L-histidine or L-histidine hydrochloride. In some embodiments, the dietary product comprises isoleucine or a salt thereof, such as L-isoleucine, L-isoleucine methyl ester hydrochloride, or L-isoleucine ethyl ester hydrochloride. In some embodiments, the dietary product comprises leucine or a salt thereof, such as L-leucine, L-leucine methyl ester hydrochloride, or L-leucine ethyl ester hydrochloride. In some embodiments, the dietary product comprises lysine or a salt thereof, such as L-lysine, L-lysine hydrochloride, or L-lysine dihydrochloride. In some embodiments, the dietary product comprises methionine or a salt thereof, such as L-methionine, L-methionine methyl ester hydrochloride, or L-methionine hydrochloride.

[0381] In some embodiments, the dietary product comprises cysteine or a salt thereof, such as L-cysteine, L-cysteine hydrochloride, L-cysteine methyl ester hydrochloride, or L-cysteine ethyl ester hydrochloride. In some embodiments, a composition discloses cystine or a salt thereof, such as L-cystine. In some embodiments, the dietary product comprises phenylalanine or a salt thereof, such as L-phenylalanine, DL-phenylalanine, or L-phenylalanine methyl ester hydrochloride. In some embodiments, the dietary product comprises tyrosine or a salt thereof, such as L-tyrosine or L-tyrosine hydrochloride. In some embodiments, the dietary product comprises threonine or a salt thereof, such as L-threonine or L-threonine methyl ester hydrochloride. In some embodiments, the dietary product comprises L-tryptophan. In some embodiments, the dietary product comprises valine or a salt thereof, such as L-valine, L-valine methyl ester hydrochloride, or L-valine ethyl ester hydrochloride.

[0382] In some embodiments, the dietary product comprises arginine or a salt thereof, such as L-arginine or L-arginine hydrochloride. In some embodiments, the dietary product comprises glutamine or a salt thereof, such as L-glutamine or L-glutamine hydrochloride. In some embodiments, the dietary product comprises alanine or a salt thereof, such as L-alanine or β-

alanine. In some embodiments, the dietary product comprises aspartic acid or a salt thereof, such as L-aspartic acid, D-aspartic acid, L- or D-aspartic acid potassium salt, L- or D-aspartic acid hydrochloride salt; L- or D-aspartic acid magnesium salt, or L- or D-aspartic acid calcium salt. In some embodiments, the dietary product comprises L-asparagine. In some embodiments, the dietary product comprises glutamic acid or a salt thereof, such as L-glutamic acid or L-glutamic acid hydrochloride. In some embodiments, the dietary product comprises proline or a salt thereof, such as L-proline, L-proline hydrochloride, L-proline methyl ester hydrochloride, or L-proline ethyl ester hydrochloride.

[0383] In some embodiments, the dietary product is administered orally. In some embodiments, the dietary product is formulated as a solid (*e.g.*, a powder). In some embodiments, the dietary product is formulated as a beverage. In some embodiments, the dietary product is formulated as a solid (*e.g.*, a powder) that is reconstituted in water.

[0384] In some embodiments, the dietary product is administered via tube. In some embodiments, the dietary product is administered via nasogastric tube. In some embodiments, the dietary product is administered intravenously or parenterally.

[0385] In some embodiments, the subject is administered a therapeutically effective amount of the dietary product. In some embodiments, the therapeutically effective amount of the dietary product is from about 0.5 g/kg/day to about 1 g/kg/day. In some embodiments, the therapeutically effective amount of the dietary product is about 0.5 g/kg/day, about 0.6 g/kg/day, about 0.7 g/kg/day, about 0.8 g/kg/day, about 0.9 g/kg/day, or about 1.0 g/kg/day. In some embodiments, the therapeutically effective amount of the dietary product is about 0.8 g/kg/day.

[0386] In some embodiments, the dietary product is administered 3 to 5 times a day. In some embodiments, the dietary product is administered 3 times a day. In some embodiments, the dietary product is administered about 5 times a day.

[0387] A salt of an amino acid disclosed herein can be a pharmaceutically acceptable salt. A salt of an amino acid disclosed herein can be a nutritionally acceptable salt. In some embodiments, a nutritionally acceptable salt meets the requirements of its applicable FCC monograph. In some embodiments, a nutritionally acceptable salt meets the requirements of its applicable Joint FAO/WHO Expert Committee on Food Additives (JECFA) reports, monographs, or specifications. In some embodiments, a nutritionally acceptable salt meets the FDA requirements at 21 CFR 172.320.

Herbicidal Compositions

[0388] In some embodiments, the disclosure provides an herbicidal composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), (IVD3), (V), (VE), (VI), (VII), or (VIII) or an agriculturally acceptable salt thereof.

[0389] In some embodiments, the disclosure provides an herbicidal composition comprising a compound of Formulae (I), (IA), (IA3), (IB-N), (IB-N3), (IB-O), (IC-N), (IC-N3), (IC-O), (ID-O), (ID-S), (ID-SO2), (IE), (IF), (IG-N), (IG-N3), (IG-O), (IH-N), (IH-N3), (IH-O), (Ii-N), (Ii-N3), (IJ-N), (IJ-N3), (IK-N), (IK-N3), (IL-N), (IL-N3), (IM), (II), (IIA-C), (IIA-C3), (IIA-N), (IIA-N3), (IIB), (IIB3), (IIC), (IIC3), (IID), (III), (IV), (IVA), (IVA3), (IVB-O), (IVB-O3), (IVB-S), (IVB-S3), (IVC-S), (IVC-S3), (IVD), or (IVD3), or an agriculturally acceptable salt thereof.

[0390] "Agriculturally acceptable salt," as used herein, refers to a salt that is generally safe non-toxic, and is otherwise not undesirable to mammals, birds, crops, and other animals or plants that are not being targeted for control, and which confers suitable properties (*e.g.*, solubility) for agricultural use.

[0391] In some embodiments, the herbicidal composition further comprises an herbicidal safener, wherein the safener increases a metabolic rate of the herbicidal composition in a crop.

[0392] In some embodiments, the safener increases expression of a gene that encodes an enzyme responsible for xenobiotic degradation of the herbicidal composition in the crop. In some embodiments, the gene encodes Cytochrome P450, glutathione-S-transferase, or an ATP-binding cassette transporter.

[0393] In some embodiments, the safener is identified in a biological screen.

[0394] In some embodiments, the herbicidal composition and the safener are present in a ratio of at least 4:1 by weight (compound: safener).

[0395] In some embodiments, the safener comprises fluroxypyr-meptyl.

[0396] In some embodiments, the herbicidal composition further comprising a second herbicide. In some embodiments, the second herbicide does not inhibit HPD. In some embodiments, the second herbicide shows synergistic effects with the herbicidal composition.

[0397] In some embodiments, the second herbicide is a photosystem II inhibitor herbicide, an acetolactate synthase inhibitor, 5-enolpyruvlshikimate 3-phosphate synthase inhibitor, a very-long chain fatty acid biosynthesis inhibitor, an acetyl-coenzyme A carboxylase inhibitor, a synthetic auxin, a protoporphyrinogen oxidase inhibitor, a microtubule inhibitor, a carotenoid biosynthesis inhibitor, a glutamine synthetase inhibitor, or a photosystem I electron driver.

Methods of Treating Weeds

[0398] In some embodiments, the disclosure provides a method of controlling a weed, the method comprising contacting a weed with an herbicidal composition. In some embodiments, the disclosure provides a method of controlling a weed, the method comprising contacting a weed with an effective amount of an herbicidal composition.

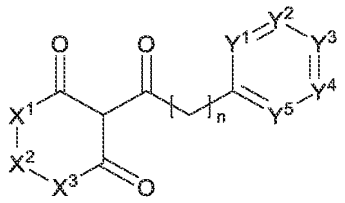
[0399] In some embodiments, the disclosure provides a method of controlling a weed, the method comprising contacting a weed with an herbicidal composition, wherein the weed is selected from the group consisting of a dicotyledonous weed and a monocotyledonous weed. In some embodiments, the weed is a dicotyledonous weed. In some embodiments, the weed is a monocotyledonous weed.

[0400] In some embodiments, the disclosure provides a method of controlling a weed, the method comprising contacting a weed with an herbicidal composition, wherein the weed has an acquired resistance to an herbicide.

[0401] In some embodiments, the disclosure provides a method of controlling a weed, the method comprising contacting a weed with an herbicidal composition, wherein the weed is an acetyl-coenzyme A carboxylase-resistant weed, an acetolactate synthase-resistant weed, a glyphosate-resistant weed, a paraquat-resistant weed, an aminopyralid + 2,4-D-resistant weed, a picloram-resistant weed, a 2,4-dichlorophenoxyacetic acid-resistant weed, a propanil-resistant weed, a 3,4-dichloroaniline + propionic acid-resistant weed, a dichloroaniline-resistant weed, a pendimethalin-resistant weed, or a weed with a combination of any of the foregoing resistances.

EXEMPLARY EMBODIMENTS

[0402] Embodiment I-1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; or

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, or CN;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4c2} combines with R^{5c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{3c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

if $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may

be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} is Cl; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl, NO_2, or SO_2-C_{1-6} alkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

or

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C.

[0403] Embodiment I-2. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is CH_2;

X^1 is CH_2, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is $S(O_2)$, and X^3 is CH_2;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; or

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond;

R^{1a} and $R^{1a'}$ are each independently selected from H and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is aryl;

wherein the aryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2c} and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d} and $R^{1d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5a2} is H, C_{1-6} haloalkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is CH_2, then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5b2} is H, C_{1-6} haloalkyl, or NO_2;

if X^1 is CH_2, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, C_{1-6} haloalkyl, or NO_2;

if $CR^{1d}R^{1d'}$, X^2 is $S(O_2)$, and X^3 is CH_2, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, C_{1-6} haloalkyl, or NO_2;

if $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5e2} is H, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, C_{1-6} haloalkyl, or NO_2;

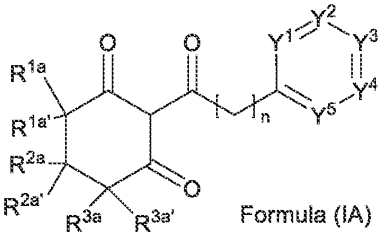
R^{2g2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, C_{1-6} haloalkyl, or NO_2;

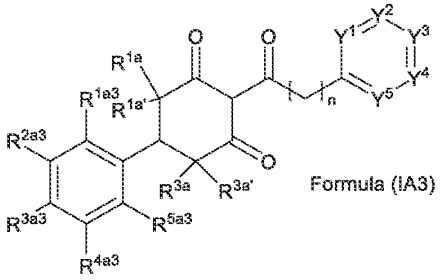
R^{5g2} is H, C_{1-6} haloalkyl, or NO_2.

[0404] Embodiment I-3. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IA)

[0405] Embodiment I-4. The compound of embodiment I-3, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

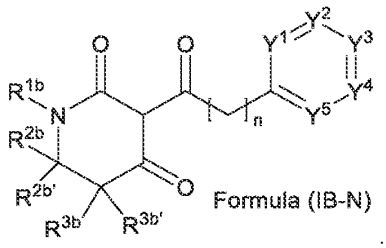


Formula (IA3)

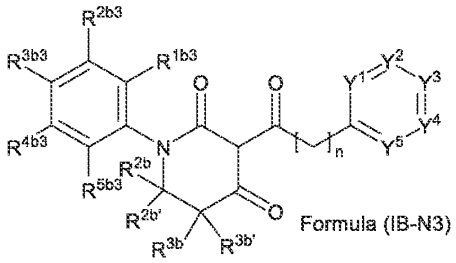
wherein R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

[0406] Embodiment I-5. The compound of embodiment I-4, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each H.

[0407] Embodiment I-6. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IB-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



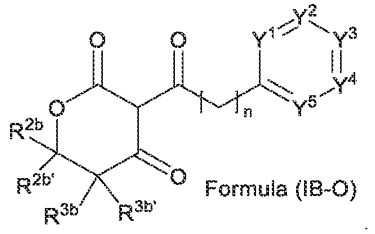
[0408] Embodiment I-7. The compound of embodiment I-6, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IB-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



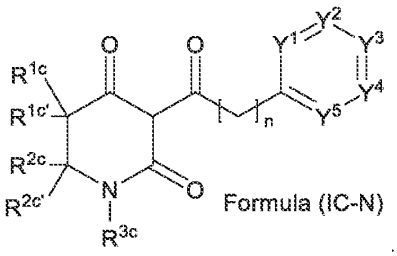
wherein R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

[0409] Embodiment I-8. The compound of embodiment I-7, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each H.

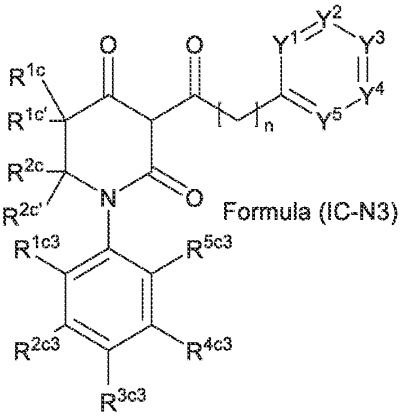
[0410] Embodiment I-9. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



[0411] Embodiment I-10. The compound of embodiment I-1 or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IC-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



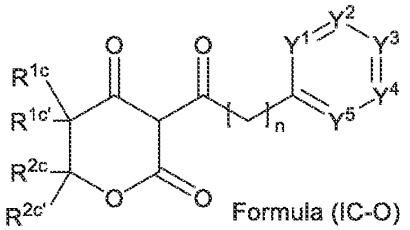
[0412] Embodiment I-11. The compound of embodiment I-10, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IC-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



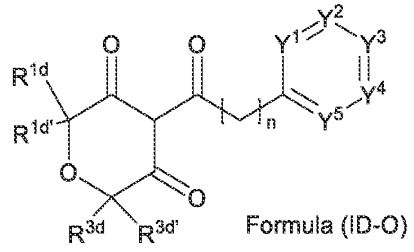
wherein R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

[0413] Embodiment I-12. The compound of embodiment I-11, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each H.

[0414] Embodiment I-13. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IC-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

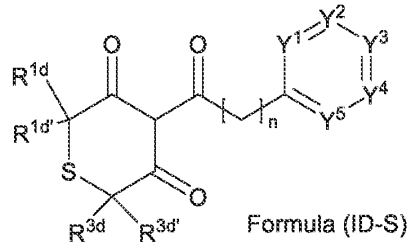


[0415] Embodiment I-14. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (ID-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



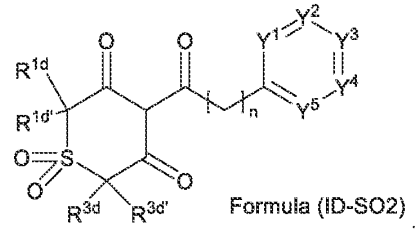
Formula (ID-O)

[0416] Embodiment I-15. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (ID-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



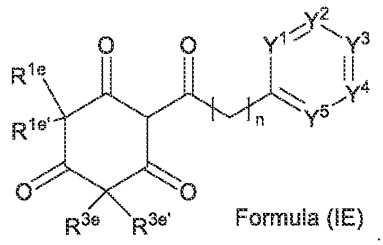
Formula (ID-S)

[0417] Embodiment I-16. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (ID-SO2), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



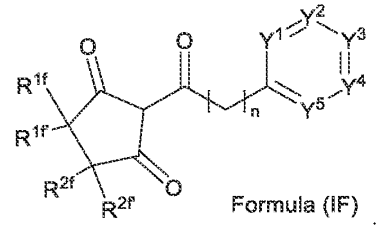
Formula (ID-SO2)

[0418] Embodiment I-17. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



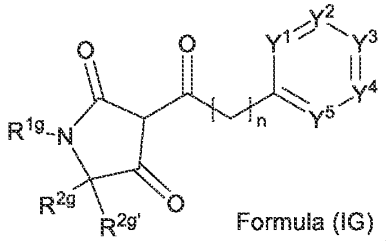
Formula (IE)

[0419] Embodiment I-18. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IF), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



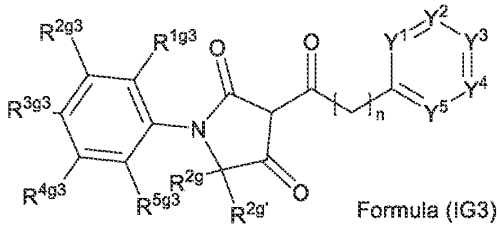
Formula (IF)

[0420] Embodiment I-19. The compounds of embodiments I-1 and I-2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IG), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG)

[0421] Embodiment I-20. The compound of embodiment I-19, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IG3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

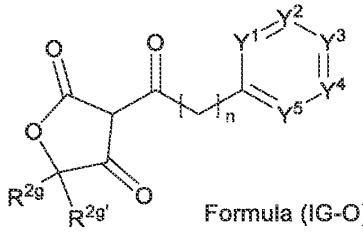


Formula (IG3)

wherein R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

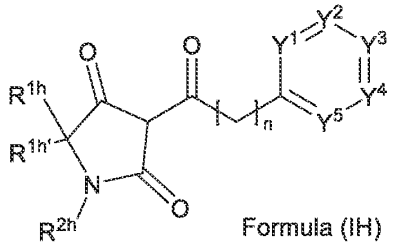
[0422] Embodiment I-21. The compound of embodiment I-20, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are H.

[0423] Embodiment I-22. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IG-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



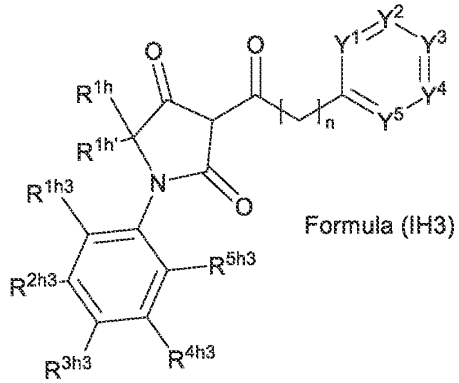
Formula (IG-O)

[0424] Embodiment I-23. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IH), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH)

[0425] Embodiment I-24. The compound of embodiment I-23, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IH3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

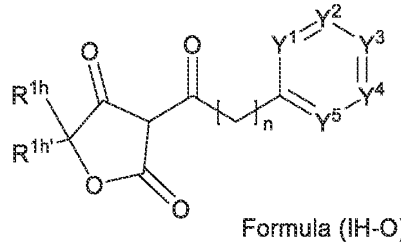


Formula (IH3)

wherein R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

[0426] Embodiment I-25. The compound of embodiment I-24, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each H.

[0427] Embodiment I-26. The compound of embodiment I-1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compounds are of Formula (IH-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-O)

[0428] Embodiment I-27. The compounds of embodiments I-1 to I-26, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein n is 0.

[0429] Embodiment I-28. The compounds of embodiments I-1 to I-26, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein n is 1.

[0430] Embodiment I-29. The compounds of embodiments I-1 to I-28, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein Y^1 is $C(NO_2)$.

[0431] Embodiment I-30. The compounds of embodiments I-1 to I-29, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein Y^3 is $C(CF_3)$.

[0432] Embodiment I-31. The compounds of embodiments I-1 to I-5, I-10 to I-18, and I-23 to I-30, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3.

[0433] Embodiment I-32. The compounds of embodiments I-1 to I-5, I-10 to I-18, and I-23 to I-30, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each H.

[0434] Embodiment I-33. The compounds of embodiments I-1 to I-3, I-6 to I-13, I-18 to I-22, and I-27 to I-32, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each CH_3.

[0435] Embodiment I-34. The compounds of embodiments I-1 to I-3, I-6 to I-13, I-18 to I-22, and I-27 to I-32, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$ are CH_3 and H respectively, R^{2b} and $R^{2b'}$ are CH_3 and H respectively, R^{2c}

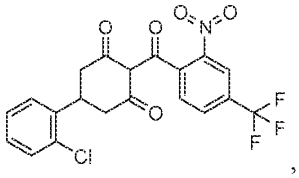
and $R^{2c'}$ are CH_3 and H respectively, R^{2f} and $R^{2f'}$ are CH_3 and H respectively, or R^{2g} and $R^{2g'}$ are CH_3 and H respectively.

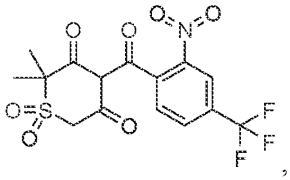
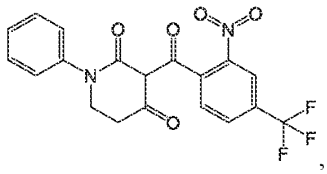
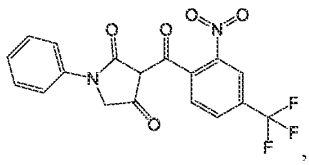
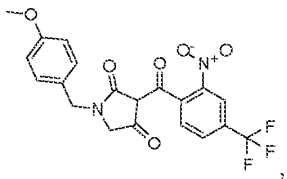
[0436] Embodiment I-35. The compounds of embodiments I-1 to I-3, I-6 to I-13, I-18 to I-22, and I-27 to I-32, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each H.

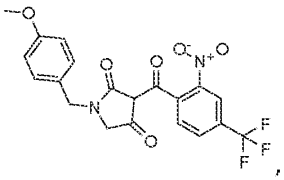
[0437] Embodiment I-36. The compounds of embodiments I-1 to I-9, I-14 to I-17, and I-27 to I-35, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, or R^{3e} and $R^{3e'}$ are each CH_3.

[0438] Embodiment I-37. The compounds of embodiments I-1 to I-9, I-14 to I-17, and I-27 to I-35 or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, or R^{3e} and $R^{3e'}$ are each H.

[0439] Embodiment I-38. A compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, selected from the group consisting of the following Table 1 compounds: Compound Nos. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 116, 17, 18 , 19, 20, 21, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, and pharmaceutically acceptable salt and tautomers of any of the foregoing.

[0440] Embodiment I-39. A compound of the structure ,

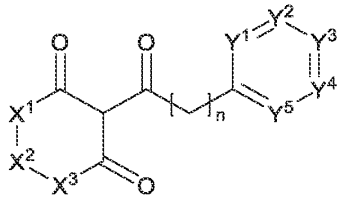
, , , or , or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.



[0441] Embodiment I-40. A compound of the structure , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0442] Embodiment I-41. A pharmaceutical composition comprising the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0443] Embodiment I-42. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O; or

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; or

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$ or N; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$ or N; and Y^5 is $C(R^{5a2})$ or N; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N, wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4c2} combines with R^{5c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{3c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

if $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$ or N; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic

ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C;

or

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and C.

[0444] Embodiment I-43. The method of embodiment I-42, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is CH_2;

X^1 is CH_2, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is $S(O_2)$, and X^3 is CH_2;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; or

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond;

R^{1a} and $R^{1a'}$ are each independently selected from H and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is aryl;

wherein the aryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2c} and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d} and $R^{1d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4a2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5a2} is H, C_{1-6} haloalkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is CH_2; then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4b2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5b2} is H, C_{1-6} haloalkyl, or NO_2;

if X^1 is CH_2, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, C_{1-6} haloalkyl, or NO_2;

if $CR^{1d}R^{1d'}$, X^2 is $S(O_2)$, and X^3 is CH_2, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, C_{1-6} haloalkyl, or NO_2;

if $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{2e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4e2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5e2} is H, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, C_{1-6} haloalkyl, or NO_2;

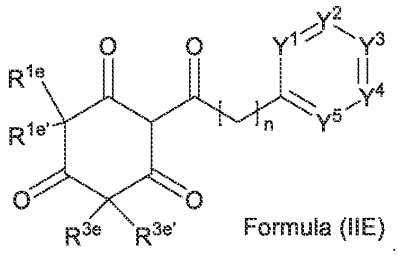
R^{2g2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5g2} is H, C_{1-6} haloalkyl, or NO_2.

[0445] Embodiment I-44. The methods of embodiments I-42 and I-43, wherein the compounds are of Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIE)

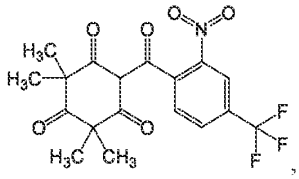
[0446] Embodiment I-45. The methods of embodiments I-42 to I-44, wherein n is 0.

[0447] Embodiment I-46. The methods of embodiments I-42 to I-45, wherein Y^1 is $C(NO_2)$.

[0448] Embodiment I-47. The methods of embodiments I-42 to I-46, wherein Y^3 is $C(CF_3)$.

[0449] Embodiment I-48. The methods of embodiments I-42 to I-47, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3.

[0450] Embodiment I-49. The methods of embodiments I-42 to I-48, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, or R^{3e} and $R^{3e'}$ are each CH_3.

[0451] Embodiment I-50. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound, wherein the compound is , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0452] Embodiment I-51. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0453] Embodiment I-52. Use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering to the subject an effective amount of the compound of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG), Formula (IG3), Formula (IG-O), Formula (IH), Formula (IH3), Formula (IH-O), Formula (II), Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0454] Embodiment I-53. Use of the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering to the subject an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0455] Embodiment I-54. Use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof,

wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG), Formula (IG3), Formula (IG-O), Formula (IH), Formula (IH3), Formula (IH-O), Formula (II), Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0456] Embodiment I-55. Use of the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof,

wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

[0457] Embodiment I-56. A compound for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject,

wherein the compounds are of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG), Formula (IG3), Formula (IG-O), Formula (IH), Formula (IH3), Formula (IH-O), Formula (II), Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0458] Embodiment I-57. The compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject.

[0459] Embodiment I-58. A pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein:

the method comprises administering the pharmaceutical formulation to a subject having the condition; and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG), Formula (IG3), Formula (IG-O), Formula (IH), Formula (IH3), Formula (IH-O), Formula (II), Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0460] Embodiment I-59. A pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein:

the method comprises administering the pharmaceutical formulation to a subject having the condition.

[0461] Embodiment I-60. A medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

the treatment comprises administering the medicament to a subject having the condition; and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG), Formula (IG3), Formula (IG-O), Formula (IH), Formula (IH3), Formula (IH-O), Formula (II), Formula (IIE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

[0462] Embodiment I-61. A medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of the compounds of embodiments I-1 to I-40, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

the treatment comprises administering the medicament to a subject having the condition.

[0463] Embodiment I-62. The methods of embodiments I-42 to I-51, wherein the condition is responsive to modulation or inhibition of HPD.

[0464] Embodiment I-63. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-62, wherein the condition is an inborn error of metabolism.

[0465] Embodiment I-64. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-63, wherein the inborn error of metabolism is an inborn error of tyrosine metabolism.

[0466] Embodiment I-65. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-64, wherein the inborn error of tyrosine metabolism is tyrosinemia type I, tyrosinemia type II, tyrosinemia type III, alkaptonuria, or hawkinsinuria.

[0467] Embodiment I-66. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-63, wherein the inborn error of metabolism is an inborn error of phenylalanine metabolism.

[0468] Embodiment I-67. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-66, wherein the inborn error of phenylalanine metabolism is phenylketonuria.

[0469] Embodiment I-68. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-62, wherein the condition is selected from the group consisting of myalgic encephalomyelitis, Parkinson's disease, Lewy Body dementia, mood disorders, autoimmune disorders, inflammatory disorders, neuropathic pain, refractory hypertension, low sex drive, attention-deficit/hyperactivity disorder (ADHD), sleep disorders, restless leg syndrome, obsessive-compulsive disorder (OCD), panic disorders, post-traumatic stress disorder (PTSD), substance abuse disorders, chronic constipation, tremor disorders, CoQ10 deficiency, and oculocutaneous albinism.

[0470] Embodiment I-69. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-68, further comprising administering low-protein diet to the subject, wherein the low-protein diet comprises less than about 2 g/day of protein.

[0471] Embodiment I-70. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-69, further comprising administering a dietary product to the subject.

[0472] Embodiment I-71. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-70, wherein the dietary product comprises less than 25% of a recommended dietary allowance (RDA) of tyrosine for the subject's age group, less than 25% of an RDA of phenylalanine for the subject's age group, or less than 25% of an RDA of tyrosine and phenylalanine for the subject's age group.

[0473] Embodiment I-72. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-71, wherein the RDA for the subject's age group is as determined by the Food and Nutrition Board of the Institute of Medicine.

[0474] Embodiment I-73. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-72, wherein the dietary product comprises less than 25% of an average recommended dietary intake of tyrosine for the subject's age group, less than 25% of an average recommended dietary intake of phenylalanine for the subject's age group, or less than 25% of an average recommended dietary intake of tyrosine and phenylalanine for the subject's age group.

[0475] Embodiment I-74. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-73, wherein the average recommended dietary intake is an RDA for the subject's age group is determined by the Food and Nutrition Board of the Institute of Medicine.

[0476] Embodiment I-75. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-74, wherein the dietary product comprises less than a daily recommended amount of phenylalanine and tyrosine combined.

[0477] Embodiment I-76. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-75, wherein the daily recommended amount of phenylalanine and tyrosine is 33 mg/kg/day.

[0478] Embodiment I-77. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-76, wherein the dietary product comprises less than 25% of a median dietary intake of tyrosine in a control or healthy subject of the same age group as the subject, less than 25% of a median dietary intake of phenylalanine in a control or healthy subject of the same age group as the subject or less than 25% of a median dietary intake of tyrosine and phenylalanine in a control or healthy subject of the same age group as the subject.

[0479] Embodiment I-78. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-70, wherein the dietary product is devoid of tyrosine, devoid of phenylalanine, or devoid of tyrosine and devoid of phenylalanine.

[0480] Embodiment I-79. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-78, wherein the dietary product is administered orally.

[0481] Embodiment I-80. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-79, wherein the dietary product is formulated as a solid or as a beverage.

[0482] Embodiment I-81. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-80, wherein the dietary product is administered via tube.

[0483] Embodiment I-82. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-81, wherein the dietary product is administered via nasogastric tube.

[0484] Embodiment I-83. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-82, wherein the dietary product is administered intravenously or parenterally.

[0485] Embodiment I-84. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-70 to I-84, wherein the subject is administered a therapeutically effective amount of the dietary product.

[0486] Embodiment I-85. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-84, wherein the therapeutically effective amount of the dietary product is from about 0.5 g/kg/day to about 1 g/kg/day.

[0487] Embodiment I-86. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-84, wherein the therapeutically effective amount of the dietary product is about 0.8 g/kg/day.

[0488] Embodiment I-87. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-68 to I-86, wherein the dietary product is administered with food.

[0489] Embodiment I-88. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-68 to I-87, wherein the dietary product is administered 3 times a day or 5 times a day.

[0490] Embodiment I-89. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-68 to I-88, wherein the dietary product is a sole source of amino acids for the subject.

[0491] Embodiment I-90. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-68 to I-89, wherein the dietary product is a sole source of calories for the subject.

[0492] Embodiment I-91. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-90, wherein the administering is oral or via tube.

[0493] Embodiment I-92. The method, the use, the compound, the pharmaceutical formulation, or the medicament of embodiment I-91, wherein the administering is via nasogastric tube.

[0494] Embodiment I-93. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-90, wherein the administering is intravenous.

[0495] Embodiment I-94. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-93, wherein the administering is once daily or twice daily.

[0496] Embodiment I-95. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-94, wherein the administering is with food.

[0497] Embodiment I-96. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-94, wherein the subject is in a fasted state.

[0498] Embodiment I-97. The method, the use, the compound, the pharmaceutical formulation, or the medicaments of embodiments I-42 to I-96, wherein the compound is administered in a pharmaceutical composition, wherein the pharmaceutical composition is in unit dosage form, the unit dosage form comprising a pharmaceutically acceptable excipient.

[0499] Embodiment I-98. An herbicidal composition comprising the compounds of embodiments I-1 to I-40, or an agriculturally acceptable salt thereof.

[0500] Embodiment I-99. The herbicidal composition of embodiment I-98, further comprising an herbicidal safener, wherein the safener increases a metabolic rate of the herbicidal composition in a crop.

[0501] Embodiment I-100. The herbicidal composition of embodiment I-99, wherein the safener increases expression of a gene that encodes an enzyme responsible for xenobiotic degradation of the herbicidal composition in the crop.

[0502] Embodiment I-101. The herbicidal composition of embodiment I-100, wherein the gene encodes Cytochrome P450, glutathione-S-transferase, or an ATP-binding cassette transporter.

[0503] Embodiment I-102. The herbicidal compositions of embodiments I-99 to I-101, wherein the safener is identified in a biological screen.

[0504] Embodiment I-103. The herbicidal compositions of embodiments I-99 to I-102, wherein the herbicidal composition and the safener are present in a ratio of at least 4:1 by weight (compound:safener).

[0505] Embodiment I-104. The herbicidal compositions of embodiments I-99 to I-103, wherein the safener comprises fluroxypyr-meptyl.

[0506] Embodiment I-105. The herbicidal compositions of embodiments I-98 to I-104, further comprising a second herbicide.

[0507] Embodiment I-106. The herbicidal composition of embodiment I-105, wherein the second herbicide does not inhibit HPD.

[0508] Embodiment I-107. The herbicidal compositions of embodiments I-105 and I-106, wherein the second herbicide shows synergistic effects with the herbicidal composition.

[0509] Embodiment I-108. The herbicidal compositions of embodiments I-105 to I-107, wherein the second herbicide is a photosystem II inhibitor herbicide, an acetolactate synthase inhibitor, 5-enolpyruvlshikimate 3-phosphate synthase inhibitor, a very long-chain fatty acid biosynthesis inhibitor, an acetyl-coenzyme A carboxylase inhibitor, a synthetic auxin, a protoporphyrinogen oxidase inhibitor, a microtubule inhibitor, a carotenoid biosynthesis inhibitor, a glutamine synthetase inhibitor, or a photosystem I electron driver.

[0510] Embodiment I-109. A method of controlling a weed, comprising contacting the weed with the herbicidal compositions of embodiments I-98-108.

[0511] Embodiment I-110. The method of embodiment I-109, comprising contacting the weed with an effective amount of the herbicidal composition.

[0512] Embodiment I-111. The methods of embodiments I-109 and I-110, wherein the weed is selected from the group consisting of a dicotyledonous weed and a monocotyledonous weed.

[0513] Embodiment I-112. The methods of embodiments I-109 to I-111, wherein the weed has an acquired resistance to an herbicide.

[0514] Embodiment I-113. The method of embodiment I-112, wherein the weed is an acetyl-coenzyme A carboxylase-resistant weed, an acetolactate synthase-resistant weed, a glyphosate-resistant weed, a paraquat-resistant weed, an aminopyralid + 2,4-D-resistant weed, a picloram-resistant weed, a 2,4-dichlorophenoxyacetic acid-resistant weed, a propanil-resistant weed, a 3,4-dichloroaniline + propionic acid-resistant weed, a dichloroaniline-resistant weed, a pendimethalin-resistant weed, or a weed with a combination of any of the foregoing resistances.

EXAMPLES

Biological Example 1: Nitisinone inhibits PAH-dependent tyrosine biosynthesis.

[0515] Tyrosine is a conditionally essential amino acid in cells that do not express phenylalanine hydroxylase (PAH), a tetrahydrobiopterin-dependent (BH4-dependent) enzyme that catalyzes tyrosine biosynthesis from phenylalanine. DLD1 cells expressing PAH (DLD1-PAH cells) have sufficient endogenous BH4 biosynthesis to support PAH function without the need to supplement BH4 or BH2 in the media. Thus, DLD1-PAH cells are a model system to screen for modulators of BH4 biosynthesis and PAH activity.

[0516] It was observed that nitisinone, and other triketone herbicides, inhibit DLD1-PAH cells in tyrosine-free physiological media (**FIG. 1**). DLD1-PAH cells in tyrosine-containing media as well as DLD1 cells lacking PAH (DLD1-EV (empty vector) cells) were relatively unaffected. These data suggest that the compounds inhibited PAH-dependent tyrosine biosynthesis.

[0517] **FIG. 1**: DLD1-EV or DLD1-PAH cells were seeded in 96-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with or without tyrosine, and a dilution series of the indicated triketone herbicide. Cells were then allowed to grow for 2 more days. Cell growth was determined by crystal violet staining and measuring absorbance at 595 nm.

[0518] To confirm that nitisinone inhibits PAH-dependent tyrosine synthesis, DLD1-EV or DLD1-PAH cells were cultured in media with uniformly ^{13}C-labelled phenylalanine (m+9) in

the presence and absence of nitisinone. We also treated these cells with or without exogenous unlabeled tyrosine. As expected, DLD1-EV cells cannot synthesize m+9 tyrosine, whereas DLD1-PAH cells can (**FIG. 2**). When unlabeled tyrosine is available in the media, endogenous steady-state m+9 tyrosine levels are elevated in DLD1-PAH cells, due to unlabeled tyrosine competing with m+9 tyrosine for consumption. Remarkably, nitisinone decreases steady-state levels of m+9 tyrosine in DLD1-PAH cells in media with unlabeled tyrosine and completely prevents the formation of m+9 tyrosine by DLD1-PAH cells when tyrosine is absent from the media (**FIG. 2**). Hence, nitisinone inhibits PAH-dependent tyrosine biosynthesis in cells.

[0519] **FIG. 2**: DLD1-EV and DLD1-PAH cells were seeded in 6-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with or without tyrosine, with or without 10 μM nitisinone, and universally ^{13}C-labelled phenylalanine (m+9). 24 hours later, intracellular metabolites were extracted for measurement of ^{13}C-tyrosine (m+0 to m+9) by mass spectrometry.

[0520] To understand how nitisinone inhibits PAH-dependent tyrosine biosynthesis, we tested if nitisinone directly inhibits PAH by treating A549-PAH cells with nitisinone in the presence and absence of tyrosine with BH4 supplementation (**FIG. 3**). A549-PAH growth was unaffected when tyrosine was absent, confirming that nitisinone does not directly inhibit PAH. Hence, nitisinone inhibits PAH function via an indirect mechanism.

[0521] **FIG. 3**: A549-EV or A549-PAH cells were seeded in 96-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with or without tyrosine, and a dilution series of nitisinone. Cells were then allowed to grow for 2 more days. Cell growth was determined by crystal violet staining and measuring absorbance at 595 nm.

Biological Example 2: Nitisinone compromises BH4 availability

[0522] It was explored if nitisinone prevents PAH function by compromising BH4 availability. DLD1-PAH cells were treated with nitisinone in tyrosine-free media in the presence and absence of BH4 or BH2 (**FIG. 4**). It was observed that BH4 or BH2 supplementation completely rescued DLD1-PAH cells from nitisinone when exogenous tyrosine was removed. Consistent with this, nitisinone decreased BH4 levels by about 50% in DLD1-EV cells and completely depleted BH4 levels in DLD1-PAH cells (**FIG. 5**). Furthermore, dose-dependent decreases in BH2 are seen in Kelly and SKNBE(2) cells (**FIG. 6**) (BH4 was undetectable in these cells; data not shown). These results suggest that nitisinone compromises BH4 availability.

[0523] **FIG. 4**: DLD1-PAH cells were seeded in 96-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with or without tyrosine, with the depicted concentration of BH4 or BH2 and a dilution series of nitisinone. Cells were then allowed to grow for 2 more days. Cell growth was determined by crystal violet staining and measuring absorbance at 595 nm.

[0524] **FIG. 5**: DLD1-EV and DLD1-PAH cells were seeded in 6-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with or without tyrosine, with or without 10 μM nitisinone. 24 hours later, intracellular metabolites were extracted using 20% water, 30% Acetonitrile, 50% Methanol, 0.5mM DTT, and 240 μM ascorbic acid. BH4, BH2 and 4a-hydroxy-BH4 levels were determined by mass spectrometry.

[0525] **FIG. 6**: Kelly and SKNBE(2) cells were seeded in 6-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media with the depicted concentrations of nitisinone. 24 hours later, intracellular metabolites were extracted using 20% water, 30% Acetonitrile, 50% Methanol, 0.5mM DTT, and 240 μM ascorbic acid. BH4, BH2, and 4a-hydroxy-BH4 levels were determined by mass spectrometry. BH4 was not detected in these cells.

[0526] BH4 is an essential cofactor for the aromatic amino acid hydroxylases, which include PAH, tyrosine hydroxylase and tryptophan hydroxylase. The nitric oxide synthases and alkylglycerol monooxygenase also require BH4. BH4 supports tyrosine, dopamine and serotonin neurotransmitter synthesis, endothelial function via nitric oxide, as well as being implicated in ferroptosis and immunity. BH4 availability is influenced by three pathways, namely *de novo* biosynthesis, recycling and salvage.

[0527] To understand how nitisinone compromises BH4 availability, we measured metabolites related to BH4 metabolism including biopterin and sepiapterin in DLD1-EV/PAH, Kelly and SKNBE(2) cells (**FIG. 7 and FIG. 8**). Similar to BH4 and BH2, levels of biopterin are decreased by nitisinone in DLD1-PAH cells when exogenous tyrosine is lacking (**FIG. 7**). Nitisinone also caused a dose-dependent decrease in biopterin levels in Kelly and SKNBE(2) cells (again, **FIG. 7**). On the other hand, nitisinone led to a striking elevation in intracellular sepiapterin levels (**FIG. 8**). This pattern of metabolite changes is consistent with inhibition of the enzyme sepiapterin reductase (SPR), which catalyzes the final step of *de novo* BH4

biosynthesis and the first step of BH4 salvage pathways. These data indicate that nitisinone may be an inhibitor of SPR.

[0528] **FIG. 7** and **FIG. 8**: DLD1-EV, DLD1-PAH, Kelly or SKNBE(2) cells were seeded in 6-well plates in complete media. 24 hours later, the media was removed and cells were washed with PBS, followed by the addition of media (with or without tyrosine for DLD1-EV and DLD1-PAH), with or without the depicted concentration of nitisinone. 24 hours later, intracellular metabolites were extracted using 20% water, 30% Acetonitrile, 50% Methanol, 0.5mM DTT, 240 μM ascorbic acid. Biopterin (FIG. 6) and sepiapterin (FIG. 7) levels were determined by mass spectrometry.

Biological Example 3: Nitisinone inhibits SPR activity.

[0529] To test if SPR is inhibited by nitisinone, *in vitro* biochemical assays of SPR activity were performed using recombinant human SPR protein, with a number of known SPR inhibitors as positive controls including QM385 (**FIG. 9**).

[0530] Compared to known SPR inhibitors, the triketones had equal or greater SPR inhibitory activity, as indicated by the IC_{50} values. Nitisinone potently inhibits the reduction of sepiapterin by SPR. Furthermore, the triketone herbicides tembotrione, sulcotrione and mesotrione used in agriculture, also inhibit SPR potently, indicating that triketone herbicides, as a class, are SPR inhibitors. Triketones are more potent SPR inhibitors than previously described sulfa drugs.

[0531] **FIG. 9A-9L**: Recombinant human SPR protein was incubated with 40μM sepiapterin, 100μM NADPH, 1 mg/mL BSA, and a dilution series of either a known SPR inhibitors (Xanthurenic acid, chlorpropramide, sulfamethoxazole, sulfathiazole, sulfasalazine, and QM395), a compound with no known SPR-inhibitory activity (methotrexate and pyrimethamine), or triketones (nitisinone, tembotrione, mesotrione, or sulcotrione), and the reduction of sepiapterin monitored by measuring absorbance at 420 nm every 2 minutes for 1 hour. From the measurements, the initial rates of reduction were determined and plotted and the IC_{50} value calculated (**FIG. 9A-9L**). Additional IC_{50} measurements protocols are provided in Biological Example 6.

[0532] The activity of recombinant mouse SPR protein was also assayed against nitisinone and other triketones and HPD-targeting herbicides (**FIG. 10**). The triketone herbicides including nitisinone were potent inhibitors of mouse SPR protein, indicating that multiple mammalian SPR homologs are likely to be inhibited by triketone herbicides including nitisinone.

[0533] **FIG. 10**: Recombinant mouse SPR protein was incubated with 40 μM sepiapterin, 100 μM NADPH, 1 mg/mL BSA and a dilution series of the depicted compounds at 37 degrees Celsius. Sepiapterin reduction was monitored by measuring absorbance at 420 nm every 2 minutes. Initial rates of reduction (up to 20 minutes) were determined and plotted.

Biological Example 4: Effect of Nitisinone on Neurocognitive Function

[0534] BH4 deficiency syndromes occur in humans that carry mutations in enzymes of the BH4 biosynthesis pathway, including GCH1, PTPS and SPR. These syndromes are characterized by neurocognitive impairment, since BH4 is critical for neuronal development and monoamine neurotransmitter synthesis. Hence, we reasoned that nitisinone-mediated SPR inhibition may explain why some subjects treated with nitisinone experience neurocognitive impairment, particularly since treatment initiates in early infancy and is lifelong.

[0535] To test this idea, we treated wild-type Balb/c with nitisinone. Plasma and brain sepiapterin levels were dramatically increased by nitisinone, indicating that SPR is inhibited by nitisinone *in vivo* (**FIG. 11**).

[0536] **FIG. 11**: Balb/c mice were treated with vehicle (50 mM NaHCO3, pH = 7.0) or 4 mg/kg nitisinone by oral gavage once per day from P14 onwards. Plasma and brain were harvested on P36. Metabolites were extracted using 40% methanol, 40% Acetonitrile and 20% water with 0.5% v/v formic acid. 10 μL of plasma was extracted with 190 μL of solvent. 10 mg of brain was extracted with 1 ml of solvent. Extracted samples were neutralized by the addition of a 15% ammonium bicarbonate solution (8.8 μL per 100 μL of extraction solvent). Nitisinone and sepiapterin levels were measured by mass spectrometry. LCMS analysis of the samples was performed on a Waters Acuity Premier HPLC system and Waters TQ-XS mass spectrometry system. Separation was achieved using Waters Premier Z-HILIC column with 20mM ammonium bicarbonate and 0.1% ammonium hydroxide in water as mobile phase (A) and 10% water and 90% acetonitrile as mobile phase (B). Analytes were detected in MRM mode. The acquired data was normalized to the internal standard (D6-Glutaric acid) and the plasma volume or tissue mass extracted using an in-house R script. N=10 mice per group.

[0537] We also then tested the ability of Balb/c and C57Bl6 mice to learn using a Morris Water Maze (**FIG. 12**). Strikingly, most nitisinone-treated mice displayed decreased ability to recall the position of the submerged platform compared to vehicle-treated controls (latency). Importantly, the mice swam at an equal speed, indicating the decreased recall ability represented a bone fide learning defect.

[0538] **FIG. 12**: Mice were treated with vehicle (50 mM $NaHCO_3$, pH = 7.0) or 4 mg/kg nitisinone by oral gavage once per day from P14 onwards. For Balb/c mice, Morris Water Maze training began on P42. For C57Bl6 mice, Morris Water Maze training began on P55. Morris Water Maze tests were carried out at a water temperature of 22 ± 2 °C. Mice were given three training trials per session per day in the presence of the hidden platform, by placing the mouse at the starting point facing the wall and releasing it into the pool for 120 seconds. The swimming speed and time taken for each mouse to find the submerged platform (latency) were recorded. At the end of each training session, mice were manually guided to the platform to strengthen memory for 20 seconds. The spatial probe test was carried out after 4 days of training for Balb/c mice and after 6 days of training for C57Bl6 mice. During the test, each mouse was allowed to swim freely for 120 seconds. The latency to the platform and average swimming speed were recorded using the XR-Super Maze tracking system. If the mouse failed to find the platform within 120 seconds, the escape latency was recorded as 120 seconds. The latency of each mouse on each day was normalized to its baseline latency (average latency of that mouse on days 1-3 (C57Bl6) or days 1-2 (Balb/c)). The latency of a mouse was considered to have improved if it decreased to below 100% of baseline, on the test day. N=12 mice per group.

[0539] SPR knockout mice have been reported to display abnormal behavior in the open field test. Strikingly, nitisinone treatment of wild-type Balb/c and C57Bl6 mice phenocopies this behavior (decreased time spent in central area) (**FIG. 13**). Together, these data indicate that nitisinone can modulate neurocognition in mice.

[0540] **FIG. 13**: Mice were treated with vehicle (50 mM $NaHCO_3$, pH = 7.0) or 4 mg/kg nitisinone by oral gavage once per day from P14 onwards. For Balb/c mice, the open field test was performed on P39. For C57Bl6 mice, the open field test was performed on P54. Each mouse was placed individually into the center of the apparatus and allowed to explore for 5 min. The time, number, distance, the average speed and number of entries into the central area of the apparatus was recorded using the XR-Xmaze tracking system. n=12 mice per group.

Synthetic Example 1: Synthesis of compounds 1-4, 8, 10-26, 32-70, 72, 74-82, 88-90, and 132-136

[0541] The reaction set-up was flushed with dry argon, and the following reaction was carried out under argon atmosphere. The reaction flask was charged with 1,3-diketone (1 eq) dissolved in alcohol-free chloroform. This solution was cooled to below 10°C with an ice bath.

Triethylamine (3 eq) was added with stirring through the addition funnel so that the reaction temperature remained in the range of about 5 to about 10°C. The addition funnel was rinsed with a small amount of chloroform and was charged with acyl chloride (1 eq). This acyl chloride was added dropwise, again keeping the reaction temperature in the range of about 5 to 10°C. The reaction was allowed to stir at room temperature for 1.5 hours after the addition was completed. Trimethylsilylcyanide (0.05 eq) was added in one portion, and the reaction was allowed to stir at room temperature for 24 hours. The color of the reaction mixture darkened during this time. The reaction mixture was cooled to below 15°C. with an ice bath and was kept at this temperature while 10% hydrochloric acid was added dropwise. The resulting mixture was transferred to a separatory funnel, and the lower organic phase separated and washed with water. The organic phase was placed back in the reaction flask and cooled to below 15°C. with an ice bath. Aqueous 4% sodium hydroxide was added with stirring while the reaction temperature remained below 15°C. The lower chloroform layer was separated, and the upper aqueous base layer was acidified by adding 10% hydrochloric acid. Again, the reaction temperature was kept below 15°C. during the acidification. The resulting precipitate was collected by filtration through a sintered glass funnel.

Synthetic Example 2: Synthesis of compound 9

[0542] To prepare 2-nitro-4-(trifluoromethyl)benzoyl chloride, the reaction flask was charged with 2-nitro-4-(trifluoromethyl)benzoic acid (1 eq). Thionyl chloride was added to the flask and the temperature raised to 70°C. The reaction mixture was stirred for 12 h under the reflux condition. TLC was used to confirm presence of the product. For the second, acylation step, the reaction flask was charged with 5-phenylcyclohexane-1,3-dione (1 eq) dissolved in DCM. Triethylamine (3 eq) was added with stirring. Acid chloride (1 eq) from the previous step was added drop-wise to the reaction flask. Finally, acetone cyanohydrin with triethylamine was added and the reaction was stirred overnight at room temperature. The resulting mixture was acidified with 1N HCl and the precipitate was collected by filtration and subjected to HPLC purification.

Synthetic Example 3: Synthesis of compounds 5-7

[0543] The reaction set-up was flushed with dry argon, and the following reaction was carried out under argon atmosphere. The reaction flask was charged with 1,3-diketone (1 eq) dissolved

in alcohol-free chloroform. This solution was cooled to below 10° C with an ice bath. Triethylamine (3 eq) was added with stirring through the addition funnel so that the reaction temperature remained in the range of about 5° to about 10° C. The addition funnel was rinsed with a small amount of chloroform and was charged with chloride (1 eq). This acid chloride was added dropwise, again keeping the reaction temperature in the range of about 5° to 10° C. The reaction was allowed to stir at room temperature for 1.5 hours after the addition was completed. Trimethylsilylcyanide (0.05 eq) was added in one portion, and the reaction was allowed to stir at room temperature for 22 hours. The color of the reaction mixture darkened during this time. The reaction mixture was cooled to below 15° C. with an ice bath and was kept at this temperature while 10% hydrochloric acid was added dropwise. The resulting mixture was transferred to a separatory funnel, and the lower organic phase separated and washed with water. The organic phase was dried over anhydrous Na2SO4, then concentrated to dryness.

Synthetic Example 4: Synthesis of compounds 27-28 and 30

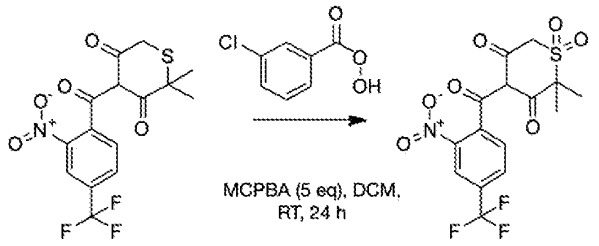
[0544] The reaction set-up was flushed with dry argon, and the following reaction was carried out under argon atmosphere. The reaction flask was charged with 1,3-cyclohexanedione (1 eq) dissolved in alcohol-free chloroform. This solution was cooled to below 10° C with an ice bath. Triethylamine (3 eq) was added with stirring through the addition funnel so that the reaction temperature remained in the range of about 5° to about 10° C. The addition funnel was rinsed with a small amount of chloroform and was charged with 2-nitro-4-trifluoromethylbenzoyl chloride (1 eq). This acid chloride was added dropwise, again keeping the reaction temperature in the range of about 5° to 10° C. The reaction was allowed to stir at room temperature for 1.5 hours after the addition was completed. Trimethylsilylcyanide (0.05 eq) was added in one portion, and the reaction was allowed to stir at room temperature for 22 hours. The color of the reaction mixture darkened during this time. The reaction mixture was cooled to below 15° C. with an ice bath and was kept at this temperature while 3% hydrochloric acid was added dropwise. The resulting mixture was transferred to a separatory funnel, and the lower organic phase separated and washed with water. The organic phase was placed back in the reaction flask and cooled to below 15° C. with an ice bath. Aqueous 5% sodium hydroxide was added with stirring while the reaction temperature remained below 15° C. The lower chloroform layer was separated, and the upper aqueous base layer was acidified by adding 3% hydrochloric acid. Again, the reaction temperature was kept below 15° C. during the acidification. The resulting

precipitate was collected by filtration through a sintered glass funnel. To deprotect the amine in compound 27 trifluoroacetic acid (2 eq) was added to solution Boc-azetidine in DCM and stirred for 15 h. Reaction mixture was evaporated.

Synthetic Example 5: Synthesis of compounds 29, 31, and 54 from their Bon-protected precursors

[0545] To a stirred solution of Bon-amine in dioxane was added 5 M HCl in dioxane at RT. The resulting reaction mixture was stirred for next 10 h. After completion of the reaction, the reaction mixture was evaporated under reduced pressure. Precipitate was washed MTBE and dried under reduced pressure to obtain the hydrochloride.

Synthetic Example 6: Synthesis of compounds 38 and 40 from their thiotriketone precursors



[0546] To a solution of thio-triketone (1 eq) in DCM at 0°C was added MCPBA (5 eq). The reaction mixture was then stirred at room temperature for 24 h. The resulting solution was washed with aqueous solution of SO2 and organic layer was evaporated.

Synthetic Example 7: Preparation of acyl chlorides

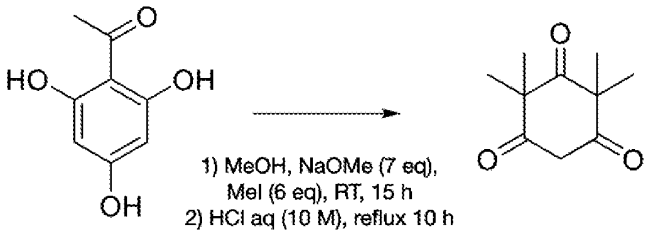
[0547] A solution of 2-nitro-4-(trifluoromethyl)benzoic acid (or other acid, as required) (1 eq) in dichloromethane was treated with oxalyl chloride (1.03 eq) and DMF (0.0001 eq). The mixture was stirred overnight. The reaction was evaporated to give a brownish oil.

Synthetic Example 8: Synthesis of 2-nitro-4-(trifluoromethyl)phenylacetic acid used as a precursor for compounds 6, 11, 24, 30-31, and 35

[0548] To a solution of 4-trifluoromethylphenyl acetic acid (1 eq) in glacial acetic acid at 0°C under an anhydrous atmosphere was added H2SO4 and 1.1 eq SO3 followed by cautious addition of 95% HNO3 (6 eq) within 10 min. The reaction mixture was then stirred at room

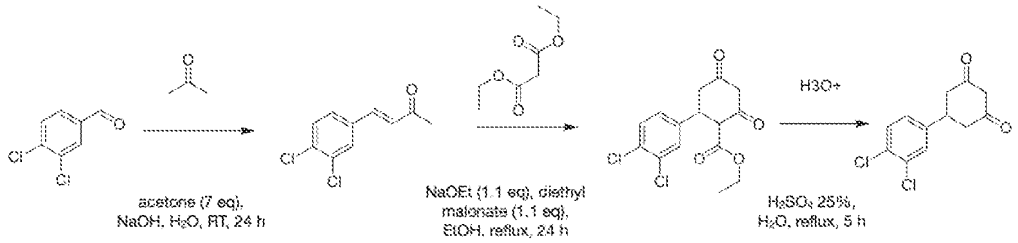
temperature for 2 h and poured into ice water. The resulting solid was filtered and washed with cold deionized water to give the desired product.

Synthetic Example 9: Synthesis of the key precursor syncarpic acid used for compounds 36 and 41-49



[0549] The obtained acetylphloroglucinol and NaOMe (7.5 eq) were dissolved in dry MeOH and methyl iodide (6.5 eq) was added. The mixture was stirred at room temperature for 24 h, then acidified with 2 M HCl. The resulting mixture was extracted with EtOAc, and the combined extracts were dried over anhydrous MgSO4, then concentrated to dryness. To the obtained residue was added 6 M HCl (2L/mol) and heated under reflux for 24 h and extracted with EtOAc.

Synthetic Example 10: Synthesis of the diketone precursors used for compounds 14-22



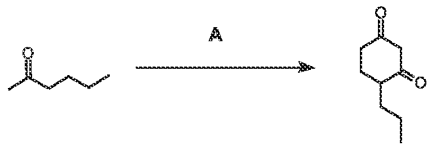
[0550] A mixture of an appropriate benzaldehyde, acetone (7.5 eq) and NaOH (1.1 eq) in water (3.2L/mol) was stirred at room temperature for 15h. The mixture was extracted with DCM, and the organic extracts were combined, dried over Na2SO4, filtered, and concentrated in vacuo to provide the title compound as a yellow crystals.

[0551] Na (1.1 eq) dissolved in EtOH(690ml/mol) and was added diethyl malonate(1.1 eq) followed by 4-(4-methylphenyl)-3-buten-2-one. The solution was heated under reflux for 6 h, allowed to cool to room temperature overnight, and filtered to provide a crude solid. The filtrate

was concentrated in vacuo to a gum which was suspended in water and washed with DCM to remove unchanged starting material and other organic-soluble impurities. The aqueous layer was concentrated in vacuo to a crude solid. This solid was combined with the crude solid obtained above, NaOH(2 eq) and H2O(750ml/mol) was added, and the resulting solution was heated under reflux for 2 h. To the cooled, basic reaction mixture was added acidificated of 25% H_2SO_4 to pH=1. The suspension which resulted was heated under reflux for 4.5 h, allowed to cool to room temperature, and filtered to provide, after trituration with toluene and drying.

[0552] The crude solid obtained above, NaOH (2 eq) and H2O (750ml/mol) was added, and the resulting solution was heated under reflux for 2 h. To the cooled, basic reaction mixture was added acidificated of 25% H_2SO_4 to pH=1. The suspension which resulted was heated under reflux for 4.5 h, allowed to cool to room temperature, and filtered to provide, after trituration with toluene and drying.

Synthetic Example 11: Synthesis of diketone intermediate for compound 77

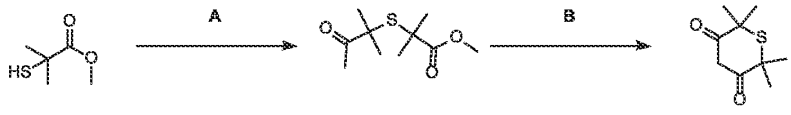


1 2

Step A:

[0553] A solution of butyl-methyl-ketone (1) (1 eq) and NaH (2.1 eq) in THF was stirred with ethyl acrylate (2.2 eq) at RT for 2 h under Ar atmosphere. The reaction mixture was acidified with 1M HCl, extracted with EtOAc, and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Yield = 65%.

Synthetic Example 12: Synthesis of diketone intermediate for compound 39



1 2 3

Step A:

[0554] To a stirred solution of methyl 2-mercapto-2-methylpropanoate (**1**) (1 eq) in THF (1L/mol), NaH (1.2 eq) was added at 0 °C. After 30 min, 3-bromo-3-methylbutan-2-one (1.1 eq) was added, and the mixture was stirred at RT for 16 h. The reaction mass was poured into saturated aq. solution of NH_4Cl and extracted with CH_2Cl_2. The organic extract was washed with water followed by brine, dried over Na_2SO_4, filtered, and concentrated. Yield = 80%.

Step B:

[0555] Na (2 eq) was dissolved in MeOH (1L/mol) and then methyl 2-methyl-2-((2-methyl-3-oxobutan-2-yl)thio)propanoate (**2**) was added. The solution was heated under reflux for 6 h. The reaction mixture was acidificated with 10% HCl to pH=2. The suspension was filtered to provide a crude solid. Yield = 60%.

Synthetic Example 13: Synthesis of diketone intermediate for compound 66

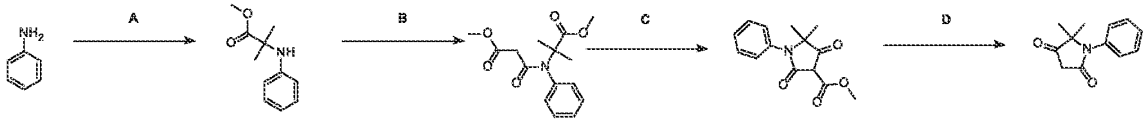


1 2

Step A:

[0556] To a cooled and stirred slurry of NaH suspension (1.65 eq) in THF (3.5L/mol) under Ar atmosphere, methyl 4-methyl-3-oxopentanoate (**1**) was added dropwise. The mixture was stirred for 15 min, and then n-BuLi(1.65 eq) was added dropwise. The solution was stirred for another 15 min, and then an acetone(1.2 eq) was added dropwise. After 30 min, the reaction mixture was poured into aq. NaOH(0.5M, 30 eq). After 2 h at 25 °C, the reaction mixture was partitioned between Et_2O and water, and the aqueous phase was extracted with Et_2O. The aqueous phase was cooled with ice and acidified until pH=6 with aq. HCl. The resulting precipitate was extracted with EA. The combined extracts were washed with water and brine, dried under Na_2SO_4, and concentrated under reduced pressure. Recrystalization of these compounds using $CHCl_3$ provided the dihydropyran-2,4-dione (**2**). Yield = 60%.

Synthetic Example 14: Synthesis of diketone intermediate for compound 72



1 2 3 4 5

Step A:

[0557] To a stirred solution of aniline (**1**) (1 eq) in DMF (1L/mol) was added K_2CO_3 (2.5 eq). After 10 min, methyl 2-bromo-2-methylpropanoate (1.1 eq) was added, and the mixture was stirred at 100 °C for 16 h. The reaction mass was poured into saturated aq. solution of NH_4Cl and extracted with CH_2Cl_2. The organic extract was washed with water followed by brine, dried over Na_2SO_4, filtered and concentrated. Yield = 60%.

Step B:

[0558] In round bottom flask was added aniline (**2**) (1 eq) dissolved in dry methylene chloride (1L/mol). Under ice-cooling and nitrogen protection conditions, triethylamine (1.5 eq) was added. After 5 min, methyl malonyl chloride (1.2 eq) was slowly added dropwise. After, the reaction was continued for 3 h. Water quenching. Extracted with methylene chloride. 1N hydrochloric acid and brine wash the organic phase. After drying over anhydrous sodium sulfate, anhydrous methylene chloride was evaporated. Yield = 50%.

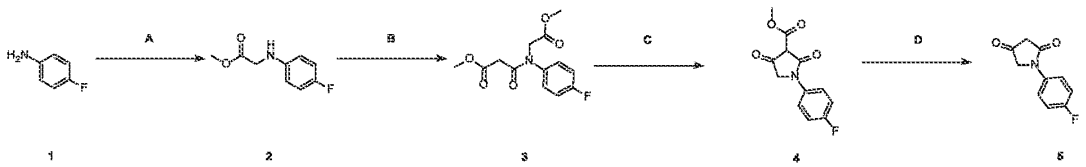
Step C:

[0559] Na(2 eq) dissolved in MeOH (1L/mol) and amido-diester (**3**) was added. The solution was heated under reflux for 6 h. The reaction mixture was acidificated of 10% HCl to pH=2. The suspension was filtered to provide a crude solid. Yield = 40%.

Step D:

[0560] To a suspension of keto-ester (**4**) in water (750mL/mol), NaOH (2 eq) was added, and the resulting solution was stirred for 2 h. To the cooled, reaction mixture was added dioxane (2L/mol) and acidificated of conc. HCl to pH=1. The suspension which resulted was stirred at 70 °C for 4 h, allowed to cool to room temperature, evaporated under reduced pressure and diluted with water, filtrated and drying. Yield = 45%.

Synthetic Example 15: Synthesis of diketone intermediate for compounds 133 and 136



Step A:

[0561] To a stirred solution of 4-fluoroaniline (**1**) (1 eq) in THF (1L/mol), NaH (1.2 eq) was added at 0 °C. After 30 min, methyl 2-bromoacetate (1.1 eq) was added, and the mixture was

stirred at RT for 16 h. The reaction mass was poured into saturated aq. solution of NH_4Cl and extracted with CH_2Cl_2. The organic extract was washed with water followed by brine, dried over Na_2SO_4, filtered and concentrated. Yield = 70%.

Step B:

[0562] In round bottom flask was added aniline (**2**) (1 eq) dissolved in dry methylene chloride (1L/mol). Under ice-cooling and nitrogen protection conditions, triethylamine (1.5 eq) was added. After 5 min, methyl malonyl chloride (1.2 eq) was slowly added dropwise. After, the reaction was continued for 3 h. Water quenching. Extracted with methylene chloride. 1N hydrochloric acid and brine wash the organic phase. After drying over anhydrous sodium sulfate, anhydrous methylene chloride was evaporated. Yield = 60%.

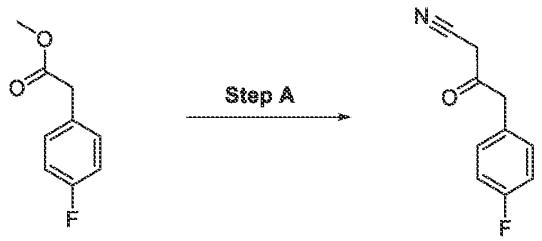
Step C:

[0563] Na(2 eq) was dissolved in MeOH (1L/mol) and amido-diester (**3**) was added. The solution was heated under reflux for 6 h. The reaction mixture was acidificated of 10% HCl to pH=2. The suspension was filtered to provide a crude solid. Yield = 40%.

Step D:

[0564] To a suspension of keto-ester (**4**) in water (750mL/mol), NaOH (2 eq) was added, and the resulting solution was stirred for 2 h. To the cooled, reaction mixture was added dioxane (2L/mol) and acidificated of conc. HCl to pH=1. The suspension which resulted was stirred at 70 °C for 4 h, allowed to cool to room temperature, evaporated under reduced pressure and diluted with water, filtrated and drying. Yield = 25%.

Synthetic Example 16: The synthesis of 4-(4-fluorophenyl)-3-oxobutanenitrile for compounds 159 and 160

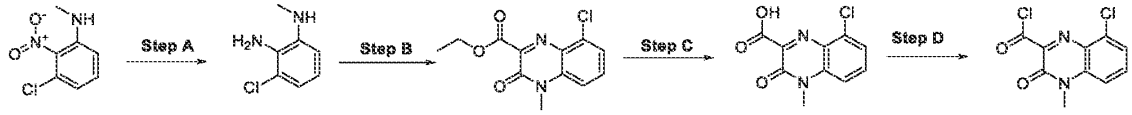


Step A:

[0565] Acetonitrile (294.54 mg, 7.18 mmol, 380.0 µl, 1.2 eq) was dissolved in tetrahydrofuran (9.0 g, 124.9 mmol, 10.0 ml, 20.87 eq). Mixture was cooled to under Ar to -78°C and *n*-butyllithium (421.76 mg, 6.58 mmol, 620.0 µl, 1.1 eq) was added dropwise, so that temperature

did not exceed -70°C. Reaction was stirred under this temperature for 30 min, and methyl 2-(4-fluorophenyl)acetate (1.01 g, 5.98 mmol) was added dropwise. Resulting mixture was warmed to room temperature, quenched with sat. solution of NH_4Cl, extracted with MTBE, dried over $MgSO_4$ and evaporated to obtain 4-(4-fluorophenyl)-3-oxobutanenitrile (832.0 mg, 85.0% purity, 3.99 mmol, 66.7% yield).

Synthetic Example 17: The synthesis of 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl chloride for compound 103



Step A: -Chloro-N1-methylbenzene-1,2-diamine

[0566] 3-Chloro-*N*-methyl-2-nitroaniline (2.5 g, 13.44 mmol) and 4,4'-bipyridine (104.88 mg, 672.04 µmol) were dissolved in dimethyl sulfoxide (27.25 g, 349.3 mmol, 25.0 ml, 25.98 eq), and (dihydroxyboranyl)boronic acid (1.45 g, 16.13 mmol) was added (highly exothermic reaction). Mixture was allowed to cool to room temperature, diluted with 100 ml of water, extracted with ethyl acetate (3*100 ml), washed with 1M NaOH, dried and evaporated under reduced pressure. 3-Chloro-*N*1-methylbenzene-1,2-diamine (1.0 g, 70.0% purity, 4.47 mmol, 33.3% yield) was used in the next step without further purification.

Step B: 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylate

[0567] 3-Chloro-*N*1-methylbenzene-1,2-diamine (1.0 g, 6.41 mmol) and 1,3-diethyl 2-oxopropanedioate (1.23 g, 7.05 mmol) were dissolved in ethanol (9.0 g, 195.47 mmol, 11.25 ml, 30.50 eq) and stirred under reflux for 2 hours. Reaction mixture was evaporated and purified by flash column chromatography to obtain ethyl 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (750.0 mg, 95.0% purity, 2.67 mmol, 41.7% yield).

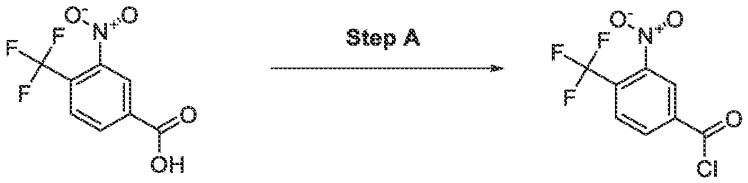
Step C: 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid

[0568] Ethyl 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (749.88 mg, 2.81 mmol) was dissolved in ethanol (2.7 g, 58.64 mmol, 3.38 ml, 20.85 eq). Sodium hydroxide (134.95 mg, 3.37 mmol), dissolved in water (3.0 g, 166.57 mmol, 3.0 ml, 59.2367632 eq), was added dropwise and resulting mixture was stirred at room temperature for 2 hours. Ethanol was evaporated under reduced pressure, and solution was acidified with 1M HCl, extracted with ethyl acetate, dried and evaporated to obtain 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (500.0 mg, 90.0% purity, 1.89 mmol, 67.1% yield).

Step D: 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl chloride

[0569] 8-Chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carboxylic acid (500.33 mg, 2.1 mmol) was dissolved in sulfuryl dichloride (8.2 g, 69.55 mmol, 5.0 ml, 33.17 eq) and stirred under reflux for 1 hour, evaporated and reevaporated twice with toluene to obtain 8-chloro-4-methyl-3-oxo-3,4-dihydroquinoxaline-2-carbonyl chloride (500.0 mg, 90.0% purity, 1.75 mmol, 83.5% yield).

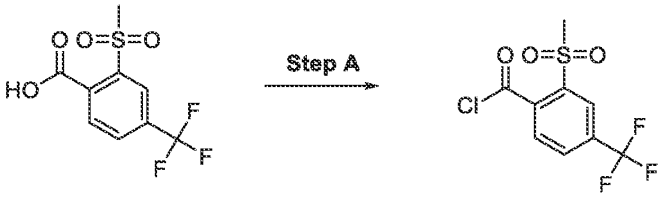
Synthetic Example 18: The synthesis of 2 3-nitro-4-(trifluoromethyl)benzoyl chloride for compounds 111, 146, and 160



Step A:

[0570] 3-nitro-4-(trifluoromethyl)benzoic acid (300.0 mg, 1.28 mmol was dissolved in sulphuryl dichloride (49.2 g, 417.29 mmol, 30.0 ml, 326.56 eq) and stirred under reflux for 2 hours, evaporated and reevaporated twice with toluene to obtain 3-nitro-4-(trifluoromethyl)benzoyl chloride (270.0 mg, 1.06 mmol, 83.3% yield), which was used in the next reaction without spectral verification.

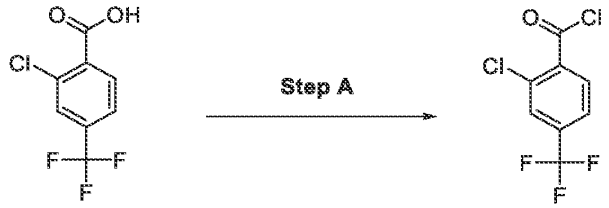
Synthetic Example 19: The synthesis of 2-methanesulfonyl-4-(trifluoromethyl)benzoyl chloride for compounds 84 and 124



Step A:

[0571] 2-methanesulfonyl-4-(trifluoromethyl)benzoic acid (500.19 mg, 1.87 mmol) was dissolved in sulphuryl dichloride (16.4 g, 139.1 mmol, 10.0 ml, 74.52 eq) and stirred under reflux for 3 hours, evaporated and reevaporated twice with toluene to obtain 2-methanesulfonyl-4-(trifluoromethyl)benzoyl chloride (500.0 mg, 90.0% purity, 1.57 mmol, 84.1% yield) as brown solid, which was used in the next reaction without spectral verification.

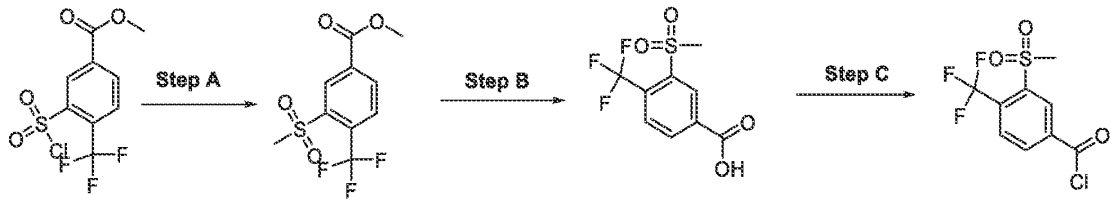
Synthetic Example 20: The synthesis of 2-chloro-4-(trifluoromethyl)benzoyl chloride for compound 125



Step A:

[0572] 2-chloro-4-(trifluoromethyl)benzoic acid (499.57 mg, 2.23 mmol) was dissolved in sulphuryl dichloride (10.51 g, 89.16 mmol, 6.41 ml, 40.0 eq) and stirred under reflux for 1.5 hours, evaporated and reevaporated twice with toluene to obtain 2-chloro-4-(trifluoromethyl)benzoyl chloride (500.0 mg, 2.06 mmol, 92.3% yield), which was used in the next reaction without spectral verification.

Synthetic Example 21: The synthesis of 3-methanesulfonyl-4-(trifluoromethyl)benzoyl chloride for compound 147



Step A: 3-methanesulfonyl-4-(trifluoromethyl)benzoate

[0573] Methyl 3-(chlorosulfonyl)-4-(trifluoromethyl)benzoate (1.0 g, 3.31 mmol) and disodium sulfite (834.0 mg, 6.62 mmol) were dissolved in water (5.0 g, 277.61 mmol, 5.0 ml, 83.80 eq) and ethanol (2.25 g, 48.87 mmol, 2.81 ml, 14.75 eq). Methyl 3-(chlorosulfonyl)-4-(trifluoromethyl)benzoate (1.0 g, 3.31 mmol) was added, and resulting mixture was heated at 50°C for 1 hour. Solvents were evaporated, and crude compound was dissolved in *N,N*-dimethylformamide (4.72 g, 64.61 mmol, 5.0 ml, 19.50 eq). Iodomethane (2.35 g, 16.55 mmol, 1.03 ml, 5.0 eq) was added in one portion. and reaction was stirred 2 hours at room temperature. Resulting mixture was diluted with 30ml of saturated $NaHCO_3$ solution and ether, and layers were separated. Organics were washed with water, dried over sodium sulfate, filtered and

concentrated under reduced pressure to obtain methyl 3-methanesulfonyl-4-(trifluoromethyl)benzoate (811.0 mg, 60.0% purity, 1.72 mmol, 52% yield)

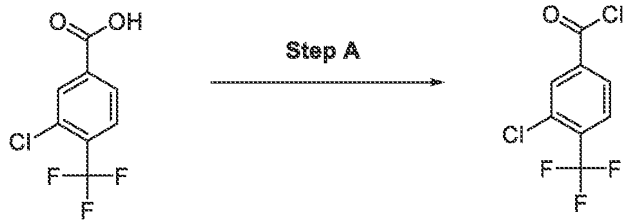
Step B: -methanesulfonyl-4-(trifluoromethyl)benzoic acid

[0574] Methyl 3-methanesulfonyl-4-(trifluoromethyl)benzoate (810.69 mg, 2.87 mmol) was dissolved in a mixture of water (10.0 g, 555.23 mmol, 10.0 ml, 193.15 eq) and methanol (4.0 g, 124.9 mmol, 5.0 ml, 43.44 eq) and lithium(1+) hydroxide (138.09 mg, 5.75 mmol) was added in one portion. Resulting mixture was stirred overnight, evaporated to dryness, acidified with 20 ml of 1M HCl, extracted with ethyl acetate (3*10 ml), washed with brine, dried over sodium sulfate and evaporated to obtain 3-methanesulfonyl-4-(trifluoromethyl)benzoic acid (700.0 mg, 70.0% purity, 1.83 mmol, 63.6% yield)

Step C: 3-methanesulfonyl-4-(trifluoromethyl)benzoyl chloride

[0575] 3-Methanesulfonyl-4-(trifluoromethyl)benzoic acid (692.78 mg, 2.58 mmol) was suspended in sulfuryl dichloride (11.48 g, 97.37 mmol, 7.0 ml, 37.66 eq), *N,N*-dimethylformamide (9.44 mg, 129.25 µmol, 10.0 µl, 0.05 eq) was added and resulting suspension was stirred under reflux for 1 hour. Reaction was evaporated under reduced pressure, reevaporated twice with toluene and 3-methanesulfonyl-4-(trifluoromethyl)benzoyl chloride (648.0 mg, 70.0% purity, 1.58 mmol, 61.2% yield) was used in the next step without purification.

Synthetic Example 22: The synthesis of 3-chloro-4-(trifluoromethyl)benzoyl chloride for compound 148

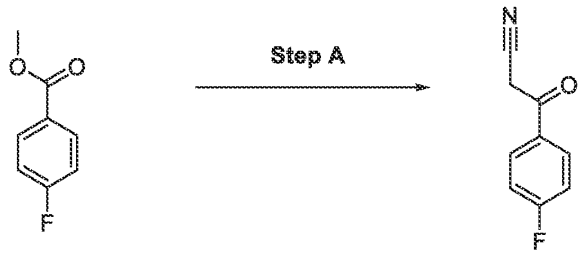


Step A:

[0576] 3-Chloro-4-(trifluoromethyl)benzoic acid (578.84 mg, 2.58 mmol) was suspended in sulfuryl dichloride (9.84 g, 83.46 mmol, 6.0 ml, 32.29 eq), *N,N*-dimethylformamide (9.44 mg, 129.21 µmol, 10.0 µl, 0.05 eq) was added and resulting suspension was stirred under reflux for 1 hour. Reaction was evaporated under reduced pressure, reevaporated twice with toluene and 3-

chloro-4-(trifluoromethyl)benzoyl chloride (550.0 mg, 70.0% purity, 1.58 mmol, 61.3% yield) was used in the next step without purification.

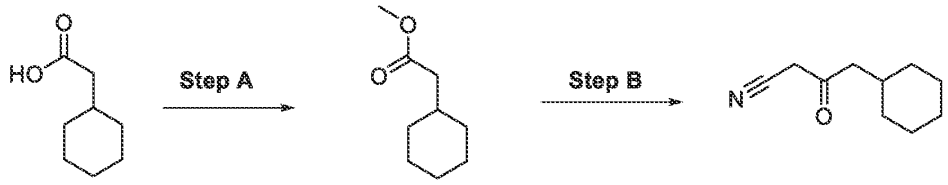
Synthetic Example 23: The synthesis of 3-(4-fluorophenyl)-3-oxopropanenitrile for compound 163



Step A:

[0577] Acetonitrile (2.0 g, 48.81 mmol, 2.58 ml, 2.5 eq) was dissolved in DCM (2.5 ml). *n*-butyllithium (2.5 g, 39.04 mmol, 3.68 ml, 2.0 eq) was added, followed by methyl 4-fluorobenzoate (3.01 g, 19.52 mmol, 2.52 ml, 1.0 eq). Resulting mixture was stirred for 20 min, and tetrahydrofuran (18.0 g, 249.8 mmol, 20.0 ml, 12.79 eq) was added. Mixture was stirred overnight at room temperature. The reaction was washed with 2M hydrochloric acid, extracted into 1M sodium hydroxide at pH-12, acidified to pH-2, extracted with DCM, dried over Na_2SO_4 and evaporated. Crude compound was purified by HPLC to obtain 3-(4-fluorophenyl)-3-oxopropanenitrile (1.2 g, 90.0% purity, 6.62 mmol, 33.9% yield).

Synthetic Example 24: The synthesis of 4-cyclohexyl-3-oxobutanenitrile for compound 165



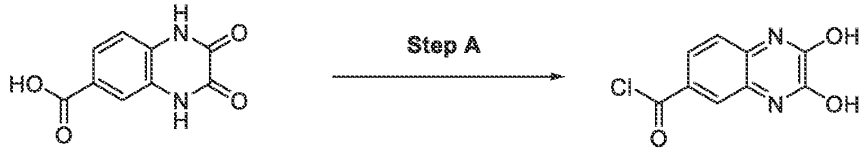
Step A: methyl 2-cyclohexylacetate

[0578] 2-Cyclohexylacetic acid (2.0 g, 14.08 mmol) was dissolved in methanol (16.0 g, 499.59 mmol, 20.0 ml, 35.49 eq). Sulfuric acid (68.95 mg, 703.8 µmol, 40.0 µl, 0.05 eq) was added, and resulting mixture was stirred under reflux overnight. Reaction mixture was quenched with triethylamine to basic pH, evaporated, dissolved in MTBE (20ml), washed with water (5ml), 1M HCl (5ml), saturated $NaHCO_3$ (5ml), brine (5ml), dried over Na_2SO_4 and evaporated to obtain methyl 2-cyclohexylacetate (1.7 g, 90.0% purity, 9.79 mmol, 69.6% yield).

Step B: 4-cyclohexyl-3-oxobutanenitrile

[0579] Acetonitrile (1.12 g, 27.23 mmol, 1.44 ml, 2.5 eq) was dissolved in tetrahydrofuran (18.0 g, 249.8 mmol, 20.0 ml, 22.93 eq) and reaction mixture was cooled to -78°C under Ar atmosphere. *N*-butyllithium (1.4 g, 21.79 mmol, 2.05 ml, 2.0 eq) was added dropwise. Resulting mixture was stirred for 30 min at -78°C, and after that methyl 2-cyclohexylacetate (1.7 g, 10.89 mmol) was added dropwise. Reaction was warmed slowly to room temperature, quenched with 40 ml of saturated NH_4Cl solution, diluted with MTBE (40ml) and extracted with MTBE (3*40ml). Combined organic layer was washed with H_2O (20ml), brine (20ml), dried over Na_2SO_4 and evaporated to obtain 4-cyclohexyl-3-oxobutanenitrile (1.4 g, 70.0% purity, 5.93 mmol, 54.4% yield).

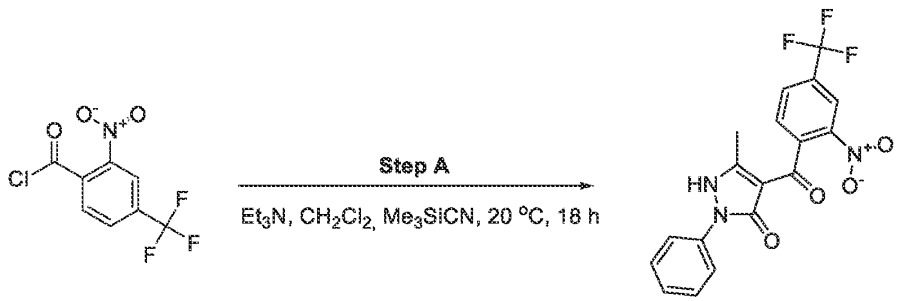
Synthetic Example 25: The synthesis of 2,3-dihydroxyquinoxaline-6-carbonyl chloride for compound 110



Step A:

[0580] 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (499.94 mg, 2.43 mmol) was dissolved in sulfuryl dichloride (14.3 g, 121.33 mmol, 8.72 ml, 50.0 eq), and stirred under reflux for 1.5 hours, evaporated and reevaporated twice with toluene (5 ml) to obtain 2,3-dihydroxyquinoxaline-6-carbonyl chloride (500.0 mg, 90.0% purity, 2.0 mmol, 82.6% yield).

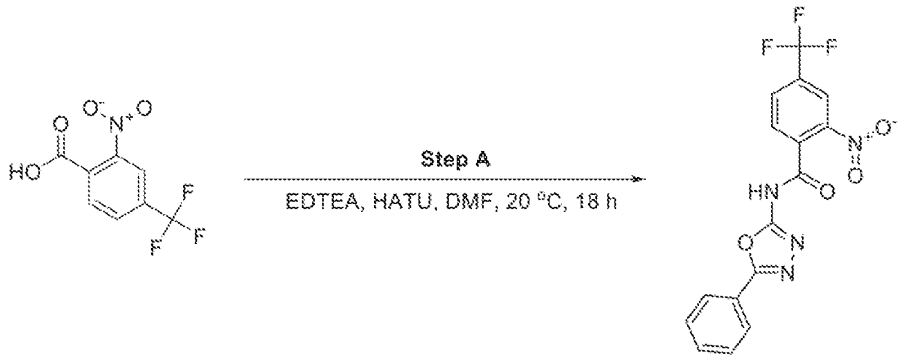
Synthetic Example 26: The synthesis of compound 166, serving as a representative example for the synthesis of compounds 84, 87, 91, 93-104, 107, 111, 113, 137, 141, 144, 147-149, 151-154, 159-161, and 163-166



Step A:

[0581] 3-Methyl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-one (74.74 mg, 429.34 µmol) was dissolved in dichloromethane (993.75 mg, 11.84 mmol, 750.0 µl, 27.57 eq). Triethylamine (130.24 mg, 1.29 mmol) was added, followed by 2-nitro-4-(trifluoromethyl)benzoyl chloride (108.61 mg, 429.34 µmol). Resulting mixture was stirred for 20 min, and trimethylsilane carbonitrile (2.13 mg, 21.47 µmol) was added. Mixture was stirred overnight at room temperature. The reaction was washed with 2M hydrochloric acid, extracted into 1M sodium hydroxide at pH-12, acidified to pH-2, extracted with DCM, dried with Na_2SO_4 and evaporated. Crude compound was purified by HPLC to obtain 5-methyl-4-[2-nitro-4-(trifluoromethyl)benzoyl]-2-phenyl-2,3-dihydro-1*H*-pyrazol-3-one (37.3 mg, 91.0% purity, 86.74 µmol, 20.2% yield).

Synthetic Example 27: The synthesis of compound 138, serving as a representative example for the synthesis of compounds 139-140, 143, 145-146, 150, and 155-156

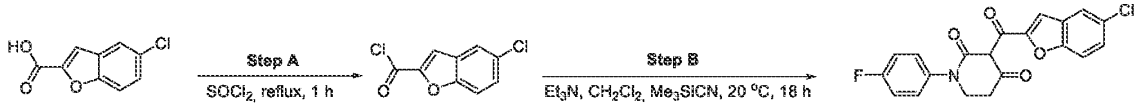


Step A:

[0582] [(dimethylamino)(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methylidene]dimethylaminyl; hexafluoro-lambda6-phosphane (121.38 mg, 319.22 µmol) was added to the solution of 2-nitro-4-(trifluoromethyl)benzoic acid (50.01 mg, 212.82 µmol) and ethylbis(propan-2-yl)amine (82.46 mg, 638.45 µmol, 110.0 µl, 3.0 eq) in *N,N*-dimethylformamide (944.0 mg, 12.92 mmol, 1.0 ml, 60.72 eq). Resulting mixture was stirred for 20 min. 5-phenyl-1,3,4-oxadiazol-2-amine (37.7 mg, 234.1 µmol) was added. Mixture was stirred overnight at room temperature. LCMS analysis showed 4.6% of conversation. Crude compound was purified by HPLC Device (Mobile Phase, Column): SYSTEM 25-25-50% 0-1-5 min H_2O/ACN, flow: 30ml/min (loading pump 4ml/min ACN) target mass 378.27 column:

Chromatorex 18 SMB100-5T 100x19mm 5um to produce 2-nitro-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)-4-(trifluoromethyl)benzamide (24.1 mg, 63.71 µmol, 29.9% yield) as beige solid.

Synthetic Example 28: The synthesis of compound 108, serving as a representative example for the synthesis of compounds 92, 105, 108-109, 112, 114, 116, 118, 120-123, 126-131, and 162



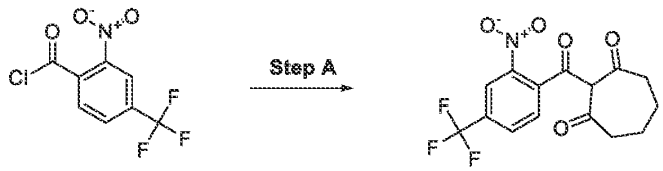
Step A:

[0583] 5-Chloro-1-benzofuran-2-carboxylic acid (235.16 mg, 1.2 mmol) was dissolved in sulfuryl dichloride (4.1 g, 34.77 mmol, 2.5 ml, 28.98 eq) and stirred under reflux for 1 hour, evaporated and reevaporated twice with toluene to obtain 5-chloro-1-benzofuran-2-carbonyl chloride (250.0 mg, 70.0% purity, 813.83 µmol, 67.8% yield).

Step B:

[0584] 1-(4-Fluorophenyl)piperidine-2,4-dione (247.99 mg, 1.2 mmol) was dissolved in DCM (2.5 ml). Triethylamine (363.0 mg, 3.59 mmol, 500.0 µl, 3.0 eq) was added, followed by 5-chloro-1-benzofuran-2-carbonyl chloride (250.0 mg, 1.17 mmol). Resulting mixture was stirred for 20 min, and trimethylsilane carbonitrile (5.93 mg, 59.88 µmol) was added. Mixture was stirred overnight at room temperature. The reaction was washed with 2M hydrochloric acid, extracted into 1M sodium hydroxide at pH-12, acidified to pH-2, extracted with DCM, dried with Na_2SO_4 and evaporated. Crude compound was purified by HPLC to obtain 3-(5-chloro-1-benzofuran-2-carbonyl)-1-(4-fluorophenyl)piperidine-2,4-dione (100.9 mg, 261.55 µmol, 21.8% yield).

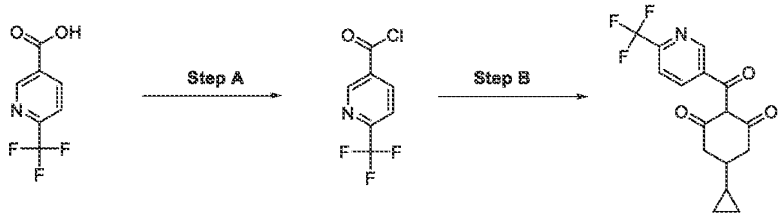
Synthetic Example 29: The synthesis of compound 85, serving as a representative example for the synthesis of compounds 85 and 124-125



Step A:

[0585] The reaction apparatus was purged with dry argon and the subsequent reaction was carried out under argon atmosphere. The reaction flask was charged with cycloheptane-1,3-dione (498.39 mg, 3.95 mmol, 450.0 µl, 1.0 eq) dissolved in dry. This solution was cooled to below 10 °C using an ice bath. Triethylamine (1.2 g, 11.86 mmol, 1.65 ml, 3.0 eq) was added with stirring via an addition funnel that the reaction temperature remained in the range of 5 ° to 10 °C. The addition funnel was washed with a small amount of chloroform and 2-nitro-4-(trifluoromethyl)benzoyl chloride (1.0 g, 3.95 mmol) was added. This solution was added dropwise, again maintaining the reaction temperature in the range of 5° to 10° C. After complete addition, the reaction mixture was stirred at room temperature for 1.5 hours. Trimethylsilane carbonitrile (19.58 mg, 197.67 µmol, 20.0 µl, 0.05 eq) was added in one portion, and the reaction mixture was stirred at room temperature for 22 hours. The color of the reaction mixture became darker during this time. The reaction mixture was cooled to a temperature below 15 ° C using an ice bath and, while maintaining this temperature, 10% hydrochloric acid solution was added dropwise. The resulting mixture was transferred to a separatory funnel, the lower organic phase was separated and washed with water. The organic phase was placed back into the reaction flask and cooled to a temperature below 15 ° C using an ice bath. Aqueous 4% sodium hydroxide was added with stirring, when the temperature of the reaction mixture was below 15 °C. The chloroform layer was separated, and the aqueous layer was acidified by adding 10% hydrochloric acid. During acidification, the reaction temperature was kept below 15 °C. A brown precipitate was formed, which, according to LCMS, had a conversion of 24.1%. purified by prep-HPLC: Device (Mobile Phase, Column): SYSTEM 40-40-65% 0-1-5 min H_2O/ACN/0.1%FA, flow: 30ml/min (loading pump 4ml/min ACN) target mass 343 column: XBridge C18 100x19mm, 5um) to obtain 2-[2-nitro-4-(trifluoromethyl)benzoyl]cycloheptane-1,3-dione (11.4 mg, 33.21 µmol, .8% yield) as white solid.

Synthetic Example 30: The synthesis of compound 83



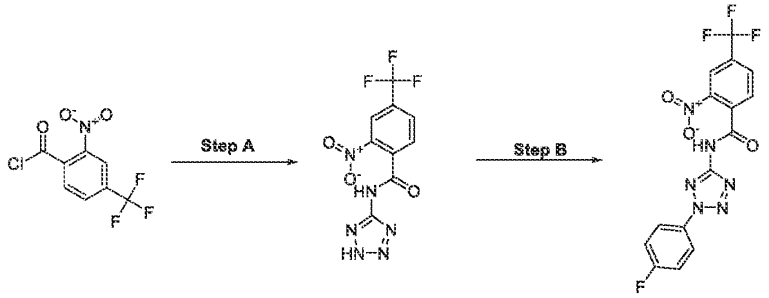
Step A:

[0586] 6-(trifluoromethyl)pyridine-3-carboxylic acid (251.59 mg, 1.32 mmol) was dissolved in sulfuryl dichloride (4.13 g, 35.03 mmol, 2.52 ml, 26.59 eq). *N,N*-dimethylformamide (4.81 mg, 65.9 µmol, 10.0 µl, 0.05 eq) was added, and mixture was stirred under reflux for 1 hour. Reaction mixture was evaporated under reduced pressure, reevaporated twice with toluene and obtained 6-(trifluoromethyl)pyridine-3-carbonyl chloride (260.0 mg, 70.0% purity, 868.52 µmol, 65.9% yield) was used in the next step without further purification.

Step B:

[0587] 5-Cyclopropylcyclohexane-1,3-dione (189.35 mg, 1.25 mmol) was dissolved in toluene (2.5 ml). Triethylamine (377.71 mg, 3.74 mmol, 450.0 µl, 3.0 eq) was added, followed by 6-(trifluoromethyl)pyridine-3-carbonyl chloride (260.0 mg, 1.24 mmol). Resulting mixture was stirred for 20 min, and trimethylsilanecarbonitrile (6.17 mg, 62.25 µmol, 10.0 µl, 0.05 eq) was added. Mixture was stirred overnight under reflux. The reaction was washed with 2M hydrochloric acid, extracted into 1M sodium hydroxide at pH-12, acidified to pH-2, extracted with DCM, dried over Na_2SO_4 and evaporated. Crude compound was purified by HPLC to obtain 5-cyclopropyl-2-[6-.(trifluoromethyl)pyridine-3-carbonyl]cyclohexane-1,3-dione (72.0 mg, 95.0% purity, 201.59 µmol, 18.7% yield).

Synthetic Example 31: The synthesis of compound 142



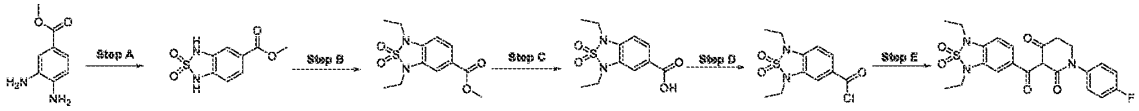
Step A: 2-nitro-N-(2H-1,2,3,4-tetrazol-5-yl)-4-(trifluoromethyl)benzamide

[0588] 1*H*-1,2,3,4-tetrazol-5-amine (400.0 mg, 4.7 mmol) and triethylamine (1.43 g, 14.11 mmol, 1.97 ml, 3.0 eq) was dissolved in dichloromethane (6.61 g, 78.69 mmol, 4.99 ml, 16.73 eq). 2-Nitro-4-(trifluoromethyl)benzoyl chloride (1.19 g, 4.7 mmol) in 4 ml of DCM was added dropwise to this mixture, and reaction was stirred under room temperature for 1 hour. Resulting mixture was washed with 1M HCl, saturated solution of $NAHCO_3$, dried and evaporated under reduced mixture. Crude 2-nitro-*N*-(2*H*-1,2,3,4-tetrazol-5-yl)-4-(trifluoromethyl)benzamide (700.0 mg, 65.0% purity, 1.51 mmol, 32% yield) was used in the next step without further purification.

Step B: N-[2-(4-fluorophenyl)-2H-1,2,3,4-tetrazol-5-yl]-2-nitro-4-(trifluoromethyl)benzamide

2-Nitro-*N*-(2*H*-1,2,3,4-tetrazol-5-yl)-4-(trifluoromethyl)benzamide (700.03 mg, 2.32 mmol), (4-fluorophenyl)boronic acid (648.88 mg, 4.63 mmol), pyridine (439.48 mg, 5.56 mmol), copper(2+) diacetate (838.44 mg, 4.63 mmol) were suspended in dichloromethane (9.28 g, 110.48 mmol, 7.0 ml, 47.6879913 eq) and stirred at room temperature for 48 hours. Resulting mixture was evaporated, washed with 1M HCl, dried under Na_2SO_4, evaporated and purified by HPLC to obtain *N*-[2-(4-fluorophenyl)-2*H*-1,2,3,4-tetrazol-5-yl]-2-nitro-4-(trifluoromethyl)benzamide (29.7 mg, 91.0% purity, 68.21 µmol, 2.9% yield).

Synthetic Example 32: The synthesis of compound 106



Step A: methyl 2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate

[0589] Methyl 3,4-diaminobenzoate (5.0 g, 30.11 mmol) and sulfamoylamine (8.67 g, 90.32 mmol) in toluene (60.98 g, 662.33 mmol, 70.33 ml, 22.0 eq) was heated at 130°C overnight. The reaction mixture was concentrated under reduced pressure to obtain methyl 2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate (1.3 g, 80.0% purity, 4.56 mmol, 15.1% yield).

Step B: methyl 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate

[0590] To solution of methyl 2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate (503.62 mg, 2.21 mmol) in *N,N*-dimethylformamide (4.84 g, 66.26 mmol, 5.13 ml, 30.0 eq) at 0°C was added sodium hydride (116.61 mg, 4.86 mmol), the suspension stay at stirring for 30 minutes. Iodoethane (1.03 g, 6.63 mmol, 530.0 µl, 3.0 eq) was added and reaction mixture was left for 12 hours at room temperature. The reaction was controlled by LCMS. Reaction mixture poured into ice, and extracted with EtOAc, the organic layers were combined and washed with brine and dried over sodium sulfate, evaporated to obtain methyl 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate (620.0 mg, 80.0% purity, 1.74 mmol, 79% yield).

Step C:1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylic acid

[0591] Methyl 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylate (619.56 mg, 2.18 mmol) dissolved in methanol (4.96 g, 154.87 mmol, 6.2 ml, 71.07 eq), sodium hydroxide in low H_2O was added (174.29 mg, 4.36 mmol) and stirring 12 hours. Then solvent

was evaporated and precipitate dissolved in water and execrated with EtOAc, water layer was acidified with $NaHSO_4$, extracted with EtOAc, dried over sodium sulfate, evaporated to obtain 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylic acid (400.0 mg, 73.0% purity, 1.08 mmol, 49.6% yield).

Step D: 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carbonyl chloride

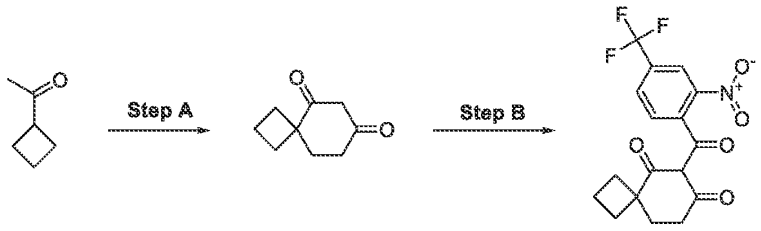
[0592] 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carboxylic acid (400.0 mg, 1.48 mmol) was dissolved in sulfuruyl dichloride (17.44 g, 147.88 mmol, 10.63 ml, 100.0 eq), reaction mixture was refluxed for 1.5 hours. Solvent was evaporated and re-evaporated with toluene (5 ml) to obtain 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carbonyl chloride (400.0 mg, 1.39 mmol, 93.7% yield) and was used in the next step without analytics and further purification.

Step E: 1,3-diethyl-5-[1-(4-fluorophenyl)-2,4-dioxopiperidine-3-carbonyl]-1,3-dihydro-2lambda6,1,3-benzothiadiazole-2,2-dione

[0593] Reaction was carried out under argon atmosphere. The reaction flask was charged with 1-(4-fluorophenyl)piperidine-2,4-dione (281.66 mg, 1.36 mmol) dissolved in anhydrous CH_2Cl_2 (5ml), the solution was cooled to a temperature below 10°C using an ice bath. Triethylamine (412.63 mg, 4.08 mmol, 570.0 µl, 3.0 eq) was added, with stirring, via a dropping funnel so that the reaction temperature remained in the range of 5° to 10°C. Then 1,3-diethyl-2,2-dioxo-1,3-dihydro-2lambda6,1,3-benzothiadiazole-5-carbonyl chloride (392.76 mg, 1.36 mmol) was added dropwise while maintaining the reaction temperature between 5° and 10°C. The reaction mixture was allowed to stir at room temperature for 1.5 hours. Trimethylsilane carbonitrile (13.48 mg, 136.1 µmol, 20.0 µl, 0.1 eq) was added and the reaction mixture was allowed to stir at room temperature for 22 hours. The reaction mixture was cooled to a temperature below 15°C using an ice bath and maintained at this temperature while adding 10% HCl dropwise. The resulting mixture was transferred to a separatory funnel, the organic phase was separated and washed with water. The organic phase was then placed back into the reaction flask and cooled to below 15°C using an ice bath. 4% aqueous sodium hydroxide solution was added with stirring until the reaction temperature remained below 15°C. The chloroform layer was separated, and the aqueous-basic layer was acidified by adding 10% HCl (the reaction temperature was maintained below 15°C during acidification). Water was extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* and purified by prep-HPLC (40-40-90% 0-2-5 min H_2O/MeOH/0.1%FA, flow: 30ml/min (loading pump 4ml/min MeOH) target mass 459 column: Chromatorex 18

SMB100-5T 100x19mm 5um) to obtain 1,3-diethyl-5-[1-(4-fluorophenyl)-2,4-dioxopiperidine-3-carbonyl]-1,3-dihydro-2lambda6,1,3-benzothiadiazole-2,2-dione (29.4 mg, 91.0% purity, 58.23 µmol, 4.3% yield).

Synthetic Example 33: The synthesis of compound 86



Step A: spiro[3.5]nonane-5,7-dione

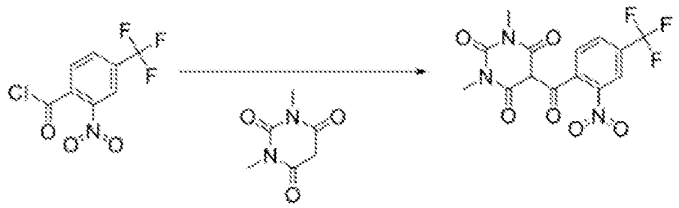
[0594] 1-Cyclobutylethan-1-one (15.0 g, 152.95 mmol, 16.63 ml, 1.0 eq) and potassium 2-methylpropan-2-olate (17.13 g, 152.95 mmol) was dissolved in dry THF (100 ml) at room temperature, cooled to 0 °C, stirred for 30 min. and ethyl prop-2-enoate (15.3 g, 152.95 mmol, 16.67 ml, 1.0 eq) was added. The temperature was raised to room temperature and stirred for 1.5 h. Saturated NH_4Cl (50 mL) was added to quench the reaction, anhydrous sodium sulfate was added, filtered, and evaporated. The residue was subjected to column chromatography to give the solid intermediate spiro[3.5]nonane-5,7-dione (600.0 mg, 96.0% purity, 3.78 mmol, 2.5% yield)

Step B: 6-[2-nitro-4-(trifluoromethyl)benzoyl]spiro[3.5]nonane-5,7-dione

[0595] The reaction apparatus was purged with dry argon and the subsequent reaction was carried out under argon atmosphere. The reaction flask was charged with spiro[3.5]nonane-5,7-dione (600.86 mg, 3.95 mmol) dissolved in anhydrous CH_2Cl_2 (5ml), the solution was cooled to below 10 °C using an ice bath. Triethylamine (1.2 g, 11.85 mmol, 1.65 ml, 3.0 eq) was added, with stirring, via a dropping funnel so that the reaction temperature remained in the range of 5° to 10°C. Then 2-nitro-4-(trifluoromethyl)benzoyl chloride (998.77 mg, 3.95 mmol) was added dropwise while maintaining the reaction temperature between 5° and 10°C. The reaction mixture was allowed to stir at room temperature for 1.5 hours. Trimethylsilane carbonitrile (39.11 mg, 394.81 µmol) was added and the reaction mixture was allowed to stir at room temperature for 22 hours. The reaction mixture was cooled to a temperature below 15°C using an ice bath and maintained at this temperature while adding 10% HCl dropwise. The resulting mixture was transferred to a separatory funnel, the organic phase was separated and washed with water. The

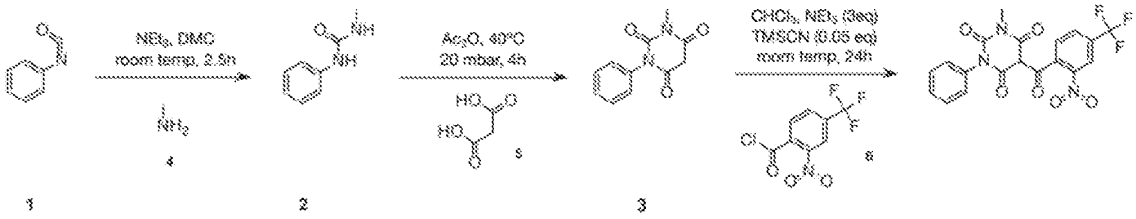
organic phase was then placed back into the reaction flask and cooled to below 15°C using an ice bath. 4% aqueous sodium hydroxide solution was added with stirring until the reaction temperature remained below 15°C. The chloroform layer was separated, and the aqueous-basic layer was acidified by adding 10% HCl (the reaction temperature was maintained below 15°C during acidification). Water was extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* and purified by prep-HPLC: Device (Mobile Phase, Column) SYSTEM 50-50-80% 0-1-5 min H_2O/ACN/0.1%FA, flow: 30ml/min loading pump 4ml/min ACN) target mass 370 column: Chromatorex 18SMB100-5T 100x19mm 5um) to obtain 6-[2-nitro-4-(trifluoromethyl)benzoyl]spiro[3.5]nonane-5,7-dione (600.0 mg, 95.0% purity, 1.54 mmol, 39.1% yield).

Synthetic Example 34: The synthesis of compound 157



[0596] The reaction apparatus was purged with dry argon and the subsequent reaction was carried out under argon atmosphere. The reaction flask was charged with 1 equiv. of 1,3-dimethylbarbituric acid dissolved in dry $CHCl_3$. This solution was cooled to below 10 °C using an ice bath. Triethylamine (3.0 eq) was added with stirring via an addition funnel that the reaction temperature remained in the range of 5 ° to 10 °C. The addition funnel was washed with a small amount of chloroform and 2-nitro-4-(trifluoromethyl)benzoyl chloride (1.0 equiv.) was added. This solution was added dropwise, again maintaining the reaction temperature in the range of 5° to 10°C. After complete addition, the reaction mixture was stirred at room temperature for 1.5 hours. Trimethylsilane carbonitrile (0.05 eq) was added in one portion, and the reaction mixture was stirred at room temperature for 24 hours. The reaction was washed with 2M hydrochloric acid, extracted into 1M sodium hydroxide at pH-12, acidified to pH-2, extracted with DCM, dried with Na_2SO_4 and evaporated. Crude compound was purified by HPLC.

Synthetic Example 35: The synthesis of compound 158



[0597] Similarly to compound 157, compound 158 was synthesized according to a slightly modified procedure outlined above.

Synthetic Example 36: The synthesis of compounds 115, 117, and 119

[0598] Compounds 115, 117, and 119 were stable O-alkyl isomers which resulted from an incomplete TMSCN-catalysed rearrangement in the final step of the reaction described above. They were purified using standard purification approach and displayed a characteristic ~6ppm shift in the 1H NMR spectra.

Analytical Method Details

[0599] Unless stated, all materials were purchased from commercial sources and used without any further treatment.

[0600] Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz or 500 MHz on the Bruker AVANCE DRX 500 or Varian UNITYplus 400 instruments. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. Chemical shifts (δ) are given in parts per million (ppm) and are listed upfield with tetramethylsilane as a reference. Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), quintets (quint) multiplets (m) and broad (br.). All assignments of NMR spectra were based on 1D NMR data. NMR data for compounds is provided in Table 1.

[0601] LCMS for all the compounds apart from compound 9 was performed using an Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm column. For compound 9, HPLC was performed using the Shim-pack Solar-C18 150*4.6mm, 5 µm column. All the samples were run at temperature of 60°C and flow rate of 3 ml/min using a gradient of 0.01 min – 1% B, 1.5 min – 100% B, 1.73 min – 100% B. Mobile phase consisted of A – water (0.1% formic acid), B – acetonitrile (0.1% formic acid). 2 min separation method was used for all the compounds apart for compound 9 for which a 20 min separation method was used. UV detection

was done at 215 nm, 254nm, and 280 nm. Mass spectra were acquired in the Electrospray ionization (ESI) mode with MS Scan range: 83 – 600 m/z. LCMS data for compounds is provided in Table 1.

LCMS Specifications and Method Details:

[0602] SUPOR_30 - Acidic_01

Application: initial purity check for all compounds with m/z up to 600

Column: Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm

Column Temperature: 60°C

Mobile phase: A – water (0.1% formic acid), B – acetonitrile (0.1% formic acid)

Flow rate: 3 ml/min

Gradient: 0.01 min – 1% B, 1.5 min – 100% B, 1.73 min – 100% B

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 600 m/z

UV detection: 215 nm, 254nm, 280 nm

[0603] POR1K_30 - Acidic_02

Application: initial purity check for all compounds with m/z up to 1000

Column: Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm

Column Temperature: 60°C

Mobile phase: A – water (0.1% formic acid), B – acetonitrile (0.1% formic acid)

Flow rate: 3 ml/min

Gradient: 0.01 min – 1% B, 1.5 min – 100% B, 1.73 min – 100% B

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 1000 m/z

UV detection: 215 nm, 254nm, 280 nm

[0604] SUPOR_30F – Acidic_03

Application: strongly retained compounds with m/z up to 1000

Column: Agilent Poroshell 120 SB-C18 4.6x30mm 2.7

Temperature: 60°C

Mobile phase: A – water (0.1% formic acid), B – acetonitrile (0.1% formic acid)

Flow rate: 3 ml/min

Gradient: 0.01 min –1% B, 1.5 min – 100% B, 2.2 min –100% B.

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 1000 m/z

UV detection: 215 nm, 254nm, 280 nm

[0605] N_SUPOR_30 - Neutral_01

Application: unstable in acidic conditions compounds

Column: Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm

Column Temperature: 60°C

Mobile phase: A – water, B – acetonitrile

Flow rate: 3 ml/min

Gradient: 0.01 min –1% B, 1.5 min – 100% B, 1.73 min – 100% B,

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 600 m/z

UV detection: 215 nm, 254nm, 280 nm

[0606] AC-GEMINI_2,3_N - Basic_01

Application: polar compounds with poor retention in acidic/neutral conditions

Column: GEMINI NX-C18 4,6x50 mm 5 Micron

Column Temperature: 25°C

Mobile phase: A – 10мМ NH4Ac in water, pH = 10, B – acetonitrile

Flow rate: 2.3 ml/min

Gradient: 0.01 min – 1% B, 1.5 min – 100% B, 1.73 min – 100% B.

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 600 m/z

UV detection: 215 nm, 254nm, 280 nm

[0607] 6min_4-6x30_1-5 - Acidic_04

Application: initial purity check for all compounds with m/z up to 1000

Column: Agilent Poroshell 120 SB-C18 4.6x30mm 2.7 µm

Column Temperature: 60°C

Mobile phase: A – water (0.1% formic acid), B – acetonitrile (0.1% formic acid)

Flow rate: 1.5 ml/min

Gradient: 0.01 min – 1% B, 5.00 min – 100% B, 5.99 min – 100% B

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 1000 m/z

UV detection: 215 nm, 254nm, 280 nm

[0608] LCMS UPLC

Column: 4.6x50mm ZORBAX SB-C18 1.8Micron

Temperature: 50°C

Mobile phase: Solvent A: CH3CN+H2O+ FA 0.1% (900:100:2)

Solvent B: H2O+FA 0.1% (1000:2)

Flow rate: 3 ml/min

Gradient:

Time	**A(%)**	**B(%)**
0,00	3,0	97,0
0,01	3,0	97,0
4,00	100,0	0,0
4,60	100,0	0,0
4,61	3,0	97,0
4,7	3,0	97,0

MS Ionization mode: Electrospray ionization (ESI)

MS Scan range: 83 – 1000 m/z

UV detection: 215 nm, 254nm, 280 nm

Biological Example 5: *In vitro* binding and inhibition of HPD and SPR of compounds

[0609] Compounds as disclosed herein are evaluated for their *in vitro* binding and inhibition of HPD and SPR. For each molecule, the IC_{50} value for HPD and the IC_{50} value for SPR are calculated and the ratio of the $IC_{50,HPD}$:$IC_{50,SPR}$ is calculated and reported as specificity. Candidate molecules with a ratio < 1 (*i.e.*, specificity <1) are considered to inhibit HPD to a greater extent than SPR. Results are reported in Table 1.

Protein purification – SPR purification

[0610] Human SPR gene with an N-terminal 6xHis-tag followed by a TEV cleavage site was cloned into a pET vector and expressed in E. coli B21 (DE3) cells grown overnight at 30°C in LB media. Cells were collected by centrifugation, lysed and the supernatant was purified using nickel affinity chromatography followed by size exclusion chromatography in 20 mM MES, pH 6.5, 150 mM NaCl and 10 µM NADP+. Fractions containing pure SPR protein as assessed by polyacrylamide gel electrophoresis were pooled and concentrated to ~50 mg/mL and stored at -80°C until used directly for the biochemical assay.

Protein purification – HPD purification

[0611] Human HPD gene with an N-terminal 6xHis-tag followed by a TEV cleavage site was cloned into a pET vector and expressed in E. coli C43 (DE3) cells grown overnight at 30°C in LB media. Cells were collected by centrifugation, lysed and the supernatant was purified using nickel affinity chromatography followed by His tag cleavage by TEV protease. Cleaved protein was obtained by reverse nickel affinity chromatography and finally size exclusion chromatography in 20 mM HEPES, pH 7.4, 150 mM NaCl. Fractions containing pure HPD protein as assessed by polyacrylamide gel electrophoresis were pooled and concentrated to ~21 mg/mL and stored at -80°C until used directly for the biochemical assay.

Protein purification – Homogentisate dioxygenase (HGD) purification

[0612] Human HGD gene with an N-terminal 6xHis-tag followed by a TEV cleavage site was cloned into a pET vector and expressed in E. coli C43 (DE3) cells grown overnight at 30°C in LB media. Cells were collected by centrifugation, lysed and the supernatant was purified using nickel affinity chromatography. Fractions containing HGD protein as assessed by polyacrylamide gel electrophoresis were pooled and concentrated to ~8 mg/mL and stored at -80°C until used directly for the biochemical assay.

In vitro biochemical activity assays – SPR activity assay

[0613] SPR activity was measured at room temperature by a UV-Vis spectroscopic method following reduction of sepiapterin with absorption maximum at 420 nm. 1µg/mL recombinant SPR was mixed with 100 µM NADPH and various concentrations of the inhibitor tested in 100 mM sodium phosphate buffer, pH6.5. Reaction was started by the addition of sepiapterin to the final concentration of 40 µM. Absorbance at 420 nm was followed for 5 min at 20 s intervals. The linear part of the slope (usually the entire duration of the reaction) was used to calculate the initial rate of reaction. IC_{50} values were derived by logistic regression analysis of reaction rates

vs inhibitor concentration (between sub nM and high μM). Experiments using inhibitors were done by incubating inhibitors with HPD for 5min prior to the activity measurement. All measurements were done in duplicates.

In vitro biochemical activity assays – HPD activity assay 1

[0614] HPD activity assay was done using purified enzymes in a buffer containing 20 mM HEPES, pH7.4, 150 mM NaCl, 100 μM FeSO4, 100 μM 4HPP (4-hydroxyphenylpyruvate), 2 mM sodium ascorbate, 0.044 mg/mL HGD and 0.0044 mg/mL HPD. HGD couples the HPD reaction product homogentisic acid to formation of maleylacetoacetic acid which absorbs strongly in the UV-Vis spectrum at around 318 nm. To ensure tight coupling a large excess of HGD to HPD is used in the assay. Reaction was started by the addition of HPD which was preincubated for 10 min with the appropriate concentration of the inhibitor tested. Reaction was followed for 10 min at 40s intervals at 318 nm. Linear part of the activity slopes was used to calculate the enzyme reaction rate. IC_{50} values were derived by logistic regression analysis of reaction rates vs inhibitor concentration (between sub nM and high μM). All measurements were done in duplicates.

In vitro biochemical activity assays – HPD activity assay 2

[0615] Alternatively, inhibitor was preincubated with HPD enzyme and 100 μM $FeSO_4$ and 2 mM sodium ascorbate. IC_{50} values obtained with this protocol were shown to correspond better to cell-based activity assay results due to 1) slow k_{on} rates of these compounds and 2) necessity for Fe during binding of the inhibitor to HPD enzyme. These IC_{50} values may reflect the actual potency of the compounds better than IC_{50} values collected with the protocol where $FeSO_4$ was not included in the preincubation mixture.

Biological Example 6: *In vivo* cell-based characterization of compounds

[0616] In addition to *in vitro* biochemical assays to measure IC_{50} of compounds, two cell-based assays were developed to characterize compound inhibition of SPR and HPD in cellular context. For *in vivo* SPR activity measurement, the DLD1-PAH cell line described above was used, which shows a growth defect when grown in tyrosine-free media in the presence of an SPR inhibitor. To assess HPD activity in vivo, a cell line was engineered with expression of TAT and HPD into DLD1. When this cell line is grown in the presence of 1 mM tyrosine it accumulates homogentisic acid, since it does not contain the rest of the tyrosine catabolism pathway. Results are reported in Table 1.

In vivo enzyme activity assays – In vivo SPR activity assay

[0617] For in vivo SPR activity measurement we use the DLD1-PAH cell line described above, which shows a growth defect when grown in tyrosine-free media in the presence of an SPR inhibitor. Briefly, cells were detached, washed and plated in 96 well plates at the density of 7.5x10^5 cells per mL in 125 µL of tyrosine-free cell growth media and an appropriate concentration of the inhibitor tested. After four days' growth, cells were fixed and stained with crystal violet to determine the cell growth. The assay is valid for all the compounds which are not toxic at the highest dose of the inhibitor tested.

In vivo enzyme activity assays – In vivo HPD activity assay

[0618] To assess HPD activity in vivo, we stably engineered expression of TAT and HPD into DLD1 cell line using a lentiviral vector. Human Myc-tagged Tat and Flag-tagged HPD were cloned into a pLV plasmid containing a puromycin resistance gene, where all the genes are expressed from a single ORF under the control of the SFFV promoter. After infection with the virus, cells were selected with 2 µg/mL puromycin for a week. When this cell line is grown in the presence of 1 mM tyrosine and 1 mM dimethyl-alpha-ketoglutarate it accumulates homogentisic acid which cannot be metabolized further due to the lack of HGD in DLD1 cell line. To set up this assay, cells were detached, washed and plated in 96 well plates at the density of 7.5x10^5 cells per mL in 125 µL of RPMI media with 10% FBS and an appropriate concentration of the inhibitor tested. After four days' growth, 100 µL of supernatant was removed alkalinized with 5 µL of 10M NaOH to induce homogentisate polymerization. The colored product absorbs in the UV-Vis spectrum with a maximum of 405nm which was detected by a spectrophotometer.

[0619] Most of the compounds' *in vitro* IC_{50}s correspond well with IC_{50}s measured in cell-based assays, suggesting that these compounds are cell-permeable and stable in tissue culture conditions for several days. Notable few exceptions are compounds based on the phenylacetic (instead of benzoic) acid which have much higher cell-based IC_{50} than in vitro IC_{50}, possibly due to metabolic instability. Compounds with very low predicted logP, *e.g.*, compound 8, also seem to do worse in cell-based assay, probably due to permeability problems.

Off-Target Toxicity (LD_{50}) in DLD1-Tat-Hpd cell line

[0620] To assess off-target toxicity of these compounds, DLD1-Tat-HPD cells were fixed and stained for viability after four days' growth with the compound, and LD_{50} was calculated. Most

compounds have LD_{50}>100 μM with a few falling between 30 and 100 μM in DLD1 cell line. This means that they are promising for further preclinical development.

Biological Example 7: Evaluation of Herbicidal Properties

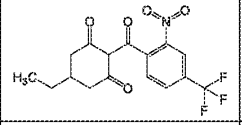
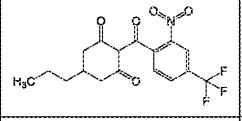
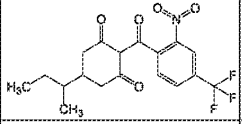
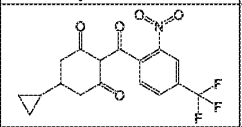
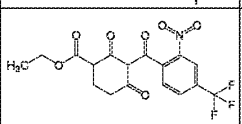
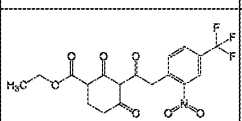
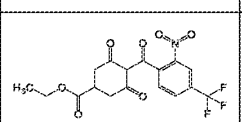
[0621] Herbicidal properties of the compounds of the present disclosure were evaluated via a bioassay on seedlings of two plant species, common poppy (*Papaver rhoeas)* and meadow foxtail grass (*Alopecurus pratensis)*. Different compounds are expected either to act as broad spectrum herbicides or to show focused herbicidal activity against only mono- or di-cotyledonous plants or against specific commercially important weed species due to the differences in binding to HPD from different species or metabolic degradation of these compounds in different species. To assess pre-germination herbicidal activity, ~10 seeds of the chosen plant species were germinated on 1.5% agar containing 100μM of the inhibitor assessed. This concentration reflects the usual herbicide application rate in the field of around 0.5-2 kg/hectare. Plates were incubated at room temperature under natural light for around 10 to 14 days while maintaining high moisture. Effects of compounds on germination and bleaching were readily apparent and were assessed visually.

Results

[0622] Results of certain compounds are shown in Table 1. LCMS results are provided as MS-ESI (m/z) [M+H]+; Retention Time (RT) in minutes (min); and Purity. Results are being collected for various compounds, as indicated by "TBD" (To Be Determined). *In vitro* columns containing two sets of values ("HPD IC_{50} [μM]" and "Selectivity") correspond to the two HPD activity assays described in Biological Example 5 above; the first set of values corresponds to HPD activity assay 1, while the second set of values corresponds to the HPD activity assay 2.

[0623] The last column of Table 1 pertains to the herbicidal properties of certain compounds. The values "0," "0.5," and "1" signify that use of the given compound resulted in bleached, partially bleached, and green seedlings respectively (each exhibiting normal germination). In contrast, "NG" is utilized to denote that no germination (or severely stunted seedlings) or gross morphological abnormalities in the root/cotyledon were observed. Results are being collected for various compounds, as indicated by "TBD" (To Be Determined).

Table 1: Compounds

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
1		358.00 - 1.44 - 95	^{1}H NMR (cdcl$_3$, 500 MHz): δ (ppm) 0.96 (t, 3H), 1.45 (p, 2H), 2.11 (m, 2H), 2.44 (d, 1H), 2.54 (dd, 1H), 2.86 (d, 1H), 7.37 (d, 1H), 7.95 (d, 1H), 8.48 (s, 1H), 16.20 (s, 1H)	0.07044	0.2573 - 0.04618	0.3 - 1.5	>160	<0.0001	>125	0 - 0
2		372.00 - 1.35 - 91	^{1}H NMR (cdcl$_3$, 500 MHz): δ (ppm) 0.92 (t, 3H), 1.38 (m, 4H), 2.11 (m, 2H), 2.43 (m, 1H), 2.53 (dd, 1H), 2.83 (dd, 1H), 7.37 (d, 1H), 7.95 (d, 1H), 8.48 (s, 1H), 16.20 (s, 1H)	0.4113	0.2126 - 0.03695	1.9 - 11.1	55	<0.0001	110.1	0 - 0
3		386.00 - 1.56 - 94	TBD	1.085	1.209 - 0.07176	0.9 - 15.1	28.83	0.005737	40.97	0 - 0
4		370.00 - 1.30 - 91	^{1}H NMR (cdcl$_3$, 500 MHz): δ (ppm) 0.16 (m, 2H), 0.53 (m, 2H), 0.70 (m, 1H), 1.36 (m, 1H), 2.29 (dd, 1H), 2.51 (dd, 1H), 2.73 (dd, 1H), 2.93 (dd, 1H), 7.36 (d, 1H), 7.94 (d, 1H), 8.48 (s, 1H), 16.22 (s, 1H)	1.552	0.2751 - 0.02527	5.6 - 61.4	>160	<0.0001	>125	0 - 0
5		402.00 - 1.35 - 91	^{1}H NMR (cdcl$_3$, 500 MHz): δ (ppm) 1.23 (t, 3H), 2.23 (m, 1H), 2.42 (m, 1H), 2.82 (m, 1H), 2.99 (m, 1H), 3.34 (dd, 1H), 4.16 (m, 2H), 7.39 (d, 1H), 7.96 (d, 1H), 8.48 (s, 1H), 16.28 (s, 1H)	6.669	0.4098 - 0.02813	16.3 - 237.1	25.6	0.0046	>160	0 - 0
6		416.20 - 1.32 - 92	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.21 (t, 3H), 2.15 (m, 2H), 2.94 (m, 1H), 3.42 (m, 1H), 3.72 (m, 1H), 4.14 (m, 2H), 4.80 (s, 2H), 7.81 (d, 1H), 8.12 (d, 1H), 8.39 (s, 1H), 16.77 (br s, 1H)	2.224	0.2491 - 0.03775	8.9 - 58.9	54.46	0.016	100	1 - 1
7		402.00 - 1.33 - 91	^{1}H NMR(cdcl$_3$, 500 MHz): δ (ppm) 1.27 (t, 3H), 2.61 (m, 2H), 3.03 (m, 1H), 3.11 (m, 2H), 4.20 (q, 2H), 7.38 (d, 1H), 7.96 (d, 1H), 8.48 (s, 1H), 16.29 (s, 1H)	6.828	0.7962 - 0.06935	8.6 - 98.5	>160	0.007799	>160	0 - 0.5

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
8		301.00 - 0.93 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.98 (p, 2H), 2.44 (m, 4H), 3.34 (s, 3H), 3.35 (s, 3H), 7.16 (d, 1H), 7.50 (s, 1H), 7.52 (d, 1H), 11.60 (br s, 1H)	0.068048	0.1626 - 0.07723	0.0 - 0.1	5.553	0.9484	>125	1 - 1
9		404.00 - 12.26 - 93	1H NMR (300 MHz in CDCl3): δ (ppm) 16.29 (s, 1H), 8.50 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.3 (m, 5H), 7.22 (d, 1H), 3.44 (m, 1H), 3.05 (d, J = 8.4 Hz, 2H), 2.62 (d, J = 8.7 Hz, 2H)	1.39	0.254 - 0.05789	5.5 - 24.0	80	0.01503	>100	0 - 0
10		436.20 - 1.32 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.62 (d, 2H), 3.04 (m, 2H), 3.41 (p, 1H), 3.81 (s, 3H), 6.76 (t, 1H), 6.82 (m, 2H), 7.29 (t, 1H), 7.40 (d, 1H), 7.97 (d, 1H), 8.50 (s, 1H), 16.28 (s, 1H)	2.96	0.77 - 0.07044	3.8 - 42.0	~80	0.013	>100	0 - 0
11		450.00 - 1.58 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.74 (dd, 1H), 2.86 (dd, 1H), 2.95 (d, 2H), 3.41 (m, 1H), 3.82 (s, 3H), 4.89 (s, 2H), 6.79 (m, 1H), 6.83 (s, 1H), 6.85 (d, 1H), 7.30 (t, 1H), 7.49 (d, 1H), 7.86 (d, 1H), 8.42 (s, 1H)	15.8	0.58 - 0.11060	27.2 - 142.9	>100	6.64	>100	1 - 1
12		424.00 - 1.48 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.59 (d, 1H), 2.61 (s, 1H), 3.01 (d, 1H), 3.03 (s, 1H), 3.43 (m, 1H), 7.06 (t, 2H), 7.19 (dd, 2H), 7.40 (d, 1H), 7.97 (d, 1H), 8.50 (s, 1H), 16.28 (s, 1H)	0.179	1.24 - 0.08589	0.1 - 2.1	48.05	0.009582	32.76	NG - 0
13		440.00 - 1.52 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.60 (m, 2H), 3.02 (m, 2H), 3.42 (m, 1H), 7.16 (d, 2H), 7.34 (d, 2H), 7.40 (d, 1H), 7.97 (d, 1H), 8.50 (s, 1H), 16.28 (s, 1H)	0.9901	1.009 - 0.06258	1.0 - 15.8	31.52	0.07136	29.42	NG - 0.5
14		474.00 - 1.71 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.58 (m, 2H), 3.02 (m, 2H), 3.41 (m, 1H), 7.07 (dd, 1H), 7.32 (d, 1H), 7.40 (d, 1H), 7.45 (d, 1H), 7.98 (d, 1H), 8.50 (s, 1H), 16.26 (s, 1H)	3.039	0.3184 - 0.05311	9.5 - 57.2	40.44	0.1234	136	NG - 0.5

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			Poppy - Grass
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	
15		472.20 - 1.32 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.64 (d, 2H), 3.07 (d, 2H), 3.52 (p, 1H), 7.36 (d, 2H), 7.41 (d, 1H), 7.64 (d, 2H), 7.98 (d, 1H), 8.50 (s, 1H), 16.30 (s, 1H)	1.696	2.015 - 0.15130	0.8 - 11.2	30.63	0.2351	47.95	NG - 0.5
16		436.00 - 1.36 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.58 (d, 1H), 2.61 (s, 1H), 3.00 (m, 1H), 3.02 (s, 1H), 3.38 (p, 1H), 3.80 (s, 3H), 6.90 (d, 2H), 7.14 (d, 2H), 7.40 (d, 1H), 7.97 (d, 1H), 8.49 (s, 1H), 16.24 (br s, 1H)	5.53	1.655 - 0.10730	3.3 - 51.5	31.1	0.0429	150.3	NG - 0
17		420.00 - 1.65 - 91	1H NMR(cdcl3, 500 MHz): δ (ppm) 2.34 (s, 3H), 2.60 (d, J=8.49 Hz, 2H), 3.03 (d, J=8.08 Hz, 2H), 3.40 (pent, J=8.67 Hz, 1H), 7.11 (d, J=7.77 Hz, 2H), 7.18 (d, J=7.77 Hz, 2H), 7.40 (d, J=7.90 Hz, 1H), 7.97 (d, J=7.91 Hz, 1H), 8.49 (s, 1H), 16.27 (s, 1H)	1.08	1.014 - 0.07020	1.1 - 15.4	39.9	0.172	43.07	NG - 0
18		440.00 - 1.46 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.64 (m, 2H), 3.01 (dd, 1H), 3.11 (dd, 1H), 3.91 (m, 1H), 7.23 (m, 2H), 7.31 (m, 1H), 7.42 (m, 2H), 7.98 (d, 1H), 8.50 (s, 1H), 16.29 (s, 1H)	7.458	0.3833 - 0.04217	19.5 - 176.9	49.04	0.02635	140.9	NG - 1
19		475.20 - 1.58 - 100	TBD	9.635	1.19 - 0.10560	8.1 - 91.2	37.32	0.2641	134.8	NG - 1
20		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
21		474.00 - 1.52 - 91	1H NMR(DMSO-d6, 500 MHz): δ (ppm) 2.62 (m, 2H), 3.02 (m, 2H), 3.77 (t, J=12.63 Hz, 1H), 7.37 (m, 1H), 7.49 (m, 1H), 7.59 (m, 1H), 7.72 (d, J=8.00 Hz, 1H), 8.25 (d, J=7.91 Hz, 1H), 8.49 (s, 1H)	2.766	N/A - 0.04369	N/A - 63.3	>10	0.00058 25	31.81	NG - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
22		475.80 - 1.56 - 100	TBD	3.489	N/A - 0.06896	N/A - 50.6	>8.3	0.05176	43.47	NG - 1
23		400.00 - 1.37 - 100	^{1}H NMR(cdcl3, 400 MHz): δ (ppm) 16.21 (s, 1H), 8.46 (s, 1H), 7.95 (d, 1H), 7.37 (d, 1H), 3.67 (m, 4H), 2.80 (s, 2H), 2.39 (s, 2H), 1.58 (m, 4H)	100	4.72 - 0.69020	21.2 - 144.9	>100	0.086	>100	0 - 0
24		414.00 - 1.32 - 100	^{1}H NMR(cdcl3, 400 MHz): δ (ppm) 16.98 (s, 1H), 8.42 (s, 1H), 7.86 (d, J= 8 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 4.85 (s, 2H), 3.73 (m, 4H). 2.75 (s, 2H), 2.61 (s, 2H), 1.63 (s, 4H)	100	3 - 0.14740	33.3 - 678.4	>100	6.35	>100	1 - 1
25		384.20 - 1.32 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.56 (m, 4H), 1.70 (m, 4H), 2.33 (s, 2H), 2.76 (s, 2H), 7.38 (d, 1H), 7.95 (d, 1H), 8.48 (s, 1H), 16.23 (s, 1H)	0.865	1.048 - 0.10380	0.8 - 8.3	>160	0.0372	>100	0 - 0
26		370.00 - 1.30 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.88 (m, 2H). 1.95 (m, 4H), 2.48 (s, 2H), 2.89 (s, 2H). 7.38 (d, 1H), 7.95 (d, 1H), 8.47 (s, 1H), 16.17 (s, 1H)	0.05016	0.2725 - 0.03950	0.2 - 1.3	>160	<0.0001	>125	0 - 0
27		371.00 - 0.95 - 95	^{1}H NMR(dmso, 500 MHz): δ (ppm) 2.86 (m. 4H). 3.78 (m. 4H), 7.60 (d. 1H), 8.18 (d, 1H). 8.42 (s, 1H), 8.71 (br s, 2H)	9.753	6.715 - 2.17260	1.5 - 4.5	>160	0.2195	>100	0 - 1
28		499.20 - 1.58 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.37 (s, 9H), 1.41 (m. 4H), 2.61 (m, 4H), 3.30 (m. 4H), 7.72 (d, 1H), 8.24 (d, 1H), 8.48 (s, 1H)	44.98	50.49 - 2.14800	0.9 - 20.9	175.6	0.04296	100	0 - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
29		397.20 - 0.89 - 100	TBD	100	100 - 5.28400	1.0 - 18.9	>100	2.134	>100	1 - 1
30		413.20 - 1.43 - 93	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.37 (m, 13H), 1.42 (m, 4H), 2.64 (m, 4H), 4.81 (s, 2H), 7.80 (d, 1H), 8.11 (d, 1H), 8.39 (s, 1H), 16.79 (s, 1H)	9.024	9.64 - 3.50200	0.9 - 2.6	29.91	27.14	31	NG - 1
31		413.20 - 0.73 - 97	TBD	22.05	2.855 - 33.6160 0	7.7 - 0.7	>160	1.424	>125	0.5 - 1
32		326.20 - 1.12 - 95	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.57 (t, 4H), 2.54 (m, 4H), 3.59 (t, 4H), 6.95 (s, 1H), 7.03 (t, 1H), 7.24 (t, 1H), 7.41 (d, 1H), 7.63 (d, 1H), 11.68 (s, 1H), 11.91 (s, 1H)	100	100 - >100	1.0 - N/A	>100	>100	>100	1 - 1
33		326.20 - 0.98 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.65 (m, 4H), 2.69 (m, 4H), 3.73 (m, 4H), 7.29 (m, 2H), 7.41 (m, 1H), 8.32 (m, 1H), 8.72 (s, 1H), 8.95 (s, 1H)	100	100 - >100	1.0 - N/A	>100	>100	>100	1 - 1
34		398.20 - 1.78 - 90	^{1}H NMR(dmso, 500 MHz): δ (ppm) 0.89 (s, 6H), 0.91 (s, 3H), 0.96 (m, 1H), 1.62 (m, 2H), 1.89 (m, 1H), 2.22 (m, 1H), 7.73 (d, 1H), 8.25 (d, 1H), 8.47 (s, 1H), 16.10 (br s, 1H)	60.57	17.34 - 0.10590	3.5 - 572.0	57.9	0.00920 1	45	0 - 0
35		412.00 - 1.48 - 95	^{1}H NMR(dmso, 500 MHz): δ (ppm) 0.96 (s, 6H), 1.12 (m, 3H), 1.9 (br, 4H), 2.6 (s, 1H), 4.8 (d, 2H), 7.8 (d, 1H), 8.1 (d, 1H), 8.39 (s, 1H), 17.3 (br, 1H)	18.74	2.776 - 0.92770	6.8 - 20.2	213.5	>100	100	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
36		400.00 - 1.30 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.28 (s, 6H), 1.59 (s, 6H), 7.45 (d, 1H), 8.00 (d, 1H), 8.49 (s, 1H), 16.71 (s, 1H)	14.34	0.1175 - 0.09466	122.0 - 151.5	>160	0.006846	>125	0 - 0
37		388.20 - 1.41 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.31 (s, 6H), 1.64 (s, 6H), 7.46 (d, 1H), 7.99 (d, 1H), 8.48 (s, 1H), 16.26 (s, 1H)	85.3	1.141 - 0.09762	74.8 - 873.8	>160	0.0182	100	0 - 0
38		408.00 - 1.25 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.33 (s, 6H), 4.01 (s, 2H), 7.30 (d, 1H), 7.96 (d, 1H), 8.25 (s, 1H)	100	0.3281 - 0.06436	304.8 - 1553.8	>160	0.05357	>160	0.5 - 1
39		404.20 - 1.44 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.39 (s, 6H), 1.70 (s, 6H), 7.45 (d, J=7.99 Hz, 1H), 7.97 (d, J=7.90 Hz, 1H), 8.48 (s, 1H)	100	0.7026 - 0.09106	142.3 - 1098.2	>160	0.02509	>160	0 - 0
40		437.00 - 1.23 - 91	^{1}H NMR(cdcl3, 500 MHz), δ (ppm) 1.56 (s, 6H), 1.89 (s, 6H), 7.45 (d, J=7.98 Hz, 1H), 8.02 (d, J=7.94 Hz, 1H), 8.50 (s, 1H)	100	1.338 - 0.17090	74.7 - 585.1	>160	0.9583	>160	1 - 1
41		379.00 - 1.40 - 91	^{1}H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.41 (s, 6H), 1.46 (s, 6H), 7.98 (m, 1H), 8.05 (m, 1H), 8.62 (s, 1H), 11.84 (s, 1H)	>100	N/A - 46.34000	N/A - >2.2	>160	0.3217	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
42		389.00 - 1.65 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.36 (s, 6H), 1.57 (s, 6H), 7.37 (d, J=7.95 Hz. 1H), 7.63 (d, J=8.09 Hz. 1H), 7.67 (s, 1H)	>100	0.8256 - 0.10540	>121 - >948.8	>160	0.00994 1	>160	0 - - 0
43		433.00 - 1.16 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.31 (s, 6H), 1.58 (s, 6H), 3.16 (s, 3H), 7.42 (m, 1H), 7.94 (d, J=8.01 Hz, 1H), 8.27 (s, 1H)	>100	1.935 - 0.61030	>52 - >163.9	>160	0.05177	>160	0 - - 0
44		399.00 - 1.07 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.36 (s, 6H), 1.57 (s, 6H), 3.12 (s, 3H), 7.44 (d, J=7.96 Hz. 1H), 7.93 (d, J=8.00 Hz. 1H), 7.98 (s, 1H)	>100	2.177 - 0.89410	>46 - >111.8	>160	0.03136	>160	0 - - 0
45		330.00 - 1.39 - 90	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.38 (s, 6H), 1.55 (s, 6H), 7.37 (d, J=9.34 Hz. 1H), 7.57 (m, 2H)	>100	1.448 - 0.63640	>69 - >157.1	>160	0.08772	>160	0 - - 0
46		329.00 - 1.42 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.40 (s, 6H), 1.59 (s, 6H), 7.54 (dd, J=6.63, 9.10 Hz, 1H), 7.65 (m, 1H), 7.99 (d, J=9.03 Hz. 1H)	>100	6.673 - 0.19270	>15 - >518.9	>160	1.104	>160	0.5 - - 0.5
47		357.00 - 1.60 - 95	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.44 (s, 6H), 1.51 (s, 6H), 7.30 (s, 2H), 7.49 (s, 1H)	>100	3.282 - 0.70040	>30 - >142.8	>160	2.135	>160	0 - - 0.5
48		356.20 - 1.39 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.44 (s, 6H), 1.53 (s, 6H), 7.77 (d, J=8.23 Hz, 1H), 8.09 (dd, J=1.96, 7.88 Hz, 1H), 8.79 (s, 1H), 15.82 (s, 1H)	>100	4.395 - 0.19350	>23 - >516.8	>160	0.2029	>160	0 - - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
49		356 - 1.294 - 96	TBD	>100	4.148 - 0.76630	>24 - >130.5	>160	1.296	>160	1 - 1
50		345.00 - 1.24 - 85	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.62 (m, 2H), 3.19 (m, 3H), 3.53 (m, 2H), 7.45 (d, 1H), 7.92 (d, 1H), 8.45 (s, 1H), 17.29 (m, 1H)	0.6882	0.408 - 0.03475	1.7 - 19.8	>160	<0.0001	>125	0 - 0
51		387.00 - 1.46 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.59 (s, 9H), 2.43 (t, 2H), 3.60 (t, 2H), 7.45 (d, 1H), 7.91 (d, 1H), 8.45 (s, 1H), 18.54 (s, 1H)	100	4.827 - 1.21800	20.7 - 82.1	65.06	0.007923	53.11	0 - 0
52		407.00 - 1.39 - 91	^{1}H NMR(cdsod, 500 MHz): δ (ppm) 2.69 (m, 1H), 3.07 (m, 1H), 3.95 (m, 2H), 7.32 (m, 5H), 7.65 (d, 1H), 8.08 (m, 1H), 8.46 (m, 1H)	22.99	0.2808 - 0.31370	81.9 - 73.3	47.76	0.008709	42.92	0 - 0.5
53		359.00 - 1.31 - 85	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.20 (m, 3H), 2.63 (m, 1H), 3.20 (m, 3H), 3.31 (m, 1H), 3.49 (m, 1H), 7.44 (d, 1H), 7.92 (d, 1H), 8.45 (s, 1H), 18.22 (m, 1H)	0.2807	0.1511 - 0.02287	1.9 - 12.3	>160	<0.0001	>125	0 - 0
54		359.20 - 1.10 - 95	^{1}H NMR(dmso, 500 MHz): δ (ppm) 1.57 (s, 6H), 2.63 (s, 2H), 4.93 (s, 1H), 7.74 (d, 1H), 8.12 (d, 1H), 8.41 (s, 1H), 11.69 (s, 1H)	16.87	60 - 4.04900	0.3 - 4.2	>160	0.1723	>160	0 - 1
55		421.20 - 1.15 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.23 (m, 3H), 2.80 (m, 2H), 3.73 (m, 1H), 3.88 (m, 1H), 7.11 (m, 2H), 7.36 (m, 2H), 7.50 (m, 1H), 7.93 (m, 1H), 8.43 (m, 1H), 17.21 (m, 1H)	60.26	8.281 - 0.78780	7.3 - 76.5	49.5	0.0169	41.11	0 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*				*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
56		421.00 - 1.59 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.36 (m, 3H), 2.75 (m, 2H), 3.91 (m, 2H), 6.96 (m, 1H), 7.18 (m, 2H), 7.37 (m, 1H), 7.48 (m, 1H), 7.93 (m, 1H), 8.44 (m, 1H)	100	50 - 0.62700	2.0 - 159.5	84.67	0.09683	160	0 - - 1
57		421.00 - 1.22 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.34 (m, 3H), 2.78 (m, 2H), 3.90 (m, 2H), 7.14 (m, 3H), 7.31 (m, 1H), 7.48 (m, 1H), 7.92 (m, 1H), 8.43 (d, 1H), 17.15 (s, 1H)	115.9	0.8332 - 0.13720	139.1 - 844.8	83.54	0.02118	120	0 - - 1
58		437.20 - 1.46 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.83 (m, 2H), 3.80 (m, 3H), 3.91 (m, 2H), 6.83 (m, 1H), 7.02 (m, 2H), 7.28 (m, 1H), 7.48 (m, 1H), 7.92 (m, 1H), 8.43 (m, 1H), 17.26 (m, 1H)	7.358	3.622 - 0.30660	2.1 - 24.7	60	0.0382	44.47	0 - - 1
59		425.20 - 1.13 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.85 (m, 2H), 3.90 (m, 2H), 7.00 (m, 1H), 7.09 (m, 1H), 7.20 (m, 1H), 7.35 (m, 1H), 7.48 (m, 1H), 7.93 (m, 1H), 8.44 (m, 1H), 17.28 (m, 1H)	87.49	2.627 - 0.13870	33.3 - 630.8	40.6	0.0112	39.26	0 - - 1
60		408.00 - 1.22 - 96	TBD	100	2.857 - 0.21430	35.0 - 466.6	>160	0.01673	>160	0 - - 1
61		421.20 - 1.17 - 75	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.62 (m, 2H), 3.43 (m, 2H), 4.62 (m, 2H), 7.13 (m, 1H), 7.34 (m, 2H), 7.40 (m, 2H), 7.49 (m, 1H), 7.95 (m, 1H), 8.46 (s, 1H), 17.38 (m, 1H)	39.56	1.304 - 0.11220	30.3 - 352.6	47.2	0.0214	>160	NG - - 0
62		413.20 - 1.27 - 90	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.15 (m, 1H), 1.30 (m, 1H), 1.49 (m, 3H), 1.79 (m, 3H), 1.91 (m, 2H), 2.61 (m, 2H), 3.44 (m, 2H), 4.43 (m, 1H), 7.45 (m, 1H), 7.92 (m, 1H), 8.44 (m, 1H), 18.26 (s, 1H)	8.204	10.63 - 1.17400	0.8 - 7.0	60.2	0.055	>160	0 - - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
63		425.00 - 1.03 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 2.10 (m, 3H), 2.80 (m, 2H), 3.72 (m, 5H), 7.78 (m, 2H), 8.23 (d, 1H), 8.47 (s, 1H), 16.96 (m, 1H)	100	100 - 0.18730	1.0 - 533.9	>160	0.1437	>160	0 - 0
64		435.20 - 1.61 - 100	TBD	3.229	N/A - 0.67890	N/A - 4.8	50.2	0.1935	>160	0 - 0
65		360.00 - 1.36 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 0.90 (t, 3H), 1.65 (p, 2H), 2.74 (dd, 1H), 2.93 (dd, 1H), 4.40 (ddd, 1H), 7.73 (d, 1H), 8.23 (dd, 1H), 8.46 (s, 1H)	0.7361	0.1112 - 0.02640	6.6 - 27.9	>160	0.00475 4	>160	0 - 0.5
66		388.00 - 1.26 - 90	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.20 (m, 6H), 1.44 (m, 6H), 7.51 (m, 1H), 7.98 (m, 1H), 8.49 (m, 1H)	100	2.303 - 0.38860	43.4 - 257.3	>160	0.00874	>160	0 - 0
67		393.00 - 1.41 - 91	^{1}H NMR(dmso, 500 MHz): δ (ppm) 4.23 (s, 2H), 6.97 (t, 1H), 7.25 (t, 2H), 7.56 (d, 2H), 7.62 (d, 1H), 8.14 (dd, 1H), 8.38 (s, 1H)	20.87	0.1173 - 0.02035	177.9 - 1025.6	>160	0.09097	>125	0.5 - 0.5
68		407.00 - 1.22 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 2.24 (m, 3H), 4.25 (m, 2H), 7.17 (m, 2H), 7.34 (m, 2H), 7.75 (m, 1H), 8.01 (m, 1H), 8.46 (m, 1H)	100	N/A - 0.22070	N/A - 453.1	>160	0.08396	>160	1 - 1
69		427.00 - 1.21 - 92	TBD	12.36	1.165 - 0.11960	10.6 - 103.3	>160	0.442	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
70		427.00 - 1.16 - 97	1H NMR(cdcl3, 500 MHz): δ (ppm) 4.17 (s, 2H), 7.29 (d, J=8.50 Hz, 2H), 7.60 (d, J=8.70 Hz, 3H), 8.13 (d, J=7.84 Hz, 1H), 8.37 (s, 1H)	13.98	0.08471 - 0.02635	165.0 - 530.6	>160	0.1657	>160	1 - 1
71		437.00 - 1.15 - 91	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 3.63 (m, 2H), 3.85 (m, 3H), 4.53 (m, 2H), 6.88 (m, 2H), 7.16 (m, 2H), 7.71 (m, 1H), 8.00 (m, 1H), 8.45 (m, 1H)	39.49	0.2126 - 0.04494	185.7 - 878.7	>160	0.2459	>160	0.5 - 1
72		421.20 - 1.27 - 100	1H NMR(DMSO-d6, 500 MHz): δ (ppm) 1.13 (s, 6H), 7.16 (d, J=7.76 Hz, 2H), 7.25 (t, J=7.41 Hz, 1H), 7.35 (t, J=7.64 Hz, 2H), 7.61 (d, J=7.97 Hz, 1H), 8.09 (d, J=7.98 Hz, 1H), 8.30 (s, 1H)	100	N/A - 0.17550	N/A - 569.8	>160	0.4505	>160	1 - 1
73		344.00 - 1.30 - 95	^{1}H NMR(cdcl3, 500 MHz): δ (ppm) 1.14 (m, 6H), 2.52 (m, 2H), 7.57 (d, 1H), 8.00 (m, 1H), 8.48 (s, 1H)	0.1169	0.1491 - 0.03743	0.8 - 3.1	>160	0.05557	>125	0 - 0.5
74		316.00 - 1.03 - 95	1H NMR(cdcl3, 500 MHz): δ (ppm) 4.87 (s, 2H), 7.13 (m, 1H), 7.62 (d,J=7.97 Hz, 1H), 8.05 (d,J=7.94 Hz, 1H), 8.51 (s, 1H)	0.4453	N/A - 0.01592	N/A - 28.0	>160	0.2616	>160	1 - 1
75		TBD - TBD - TBD	TBD	2.429	0.1784 - 0.06178	13.6 - 39.3	100	0.006454	>125	0 - 0
76		TBD - TBD - TBD	TBD	0.5507	0.1441 - 0.06252	3.82 - 8.8	59.6	0.002611	158.2	0 - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
77		TBD - TBD - TBD	TBD	0.3904	N/A - 0.01986	N/A - 19.7	>10	<0.0001	28.34	NG - 0
78		392.00 - 1.58 - 91	1H NMR(DMSO-d6, 500 MHz): δ (ppm) 1.04 (s, 6H), 1.80 (t, J=6.50 Hz, 2H), 2.73 (m, 2H), 7.99 (s, 1H), 8.51 (s, 1H)	3.421	0.1858 - 0.04838	N/A - 70.7	>160	0.00589	>160	1 - 1
79		381.00 - 1.48 - 90	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.27 (m, 6H), 1.91 (m, 2H), 2.71 (m, 2H), 7.56 (s, 2H), 16.53 (m, 1H)	5.153	N/A - 0.34230	N/A - 15.1	>160	0.07127	>160	0 - 1
80		383.00 - 1.47 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.27 (m, 6H), 1.90 (m, 2H), 2.66 (m, 2H), 7.16 (m, 1H), 7.68 (m, 1H), 16.57 (s, 1H)	0.346	N/A - 0.03212	N/A - 10.8	>160	0.00575 3	105	NG - NG
81		360.00 - 1.41 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.19 (s, 6H), 1.97 (t, J=6.24 Hz, 2H), 2.80 (t, J=6.30 Hz, 2H), 6.01 (s, 1H), 7.77 (d, J=8.95 Hz, 1H), 8.17 (d, J=8.90 Hz, 1H)	2.908	N/A - 1.25600	N/A - 2.3	>160	29.11	>160	1 - 1
82		366.00 - 1.05 - 90	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 2.37 (pent, J=6.15 Hz, 2H), 2.84 (t, J=6.44 Hz, 2H), 3.16 (m, 2H), 7.66 (d, J=7.93 Hz, 1H), 8.02 (d, J=7.97 Hz, 1H), 8.51 (s, 1H), 15.60 (s, 1H)	38.2	N/A - 0.59110	N/A - 64.6	>160	0.4707	>160	0.5 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
83		326.2 - 1.404 - 95	^{1}H NMR (600 MHz, cdcl3) δ 16.74 (s, 1H), 8.74 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 2.67 (t, J = 161.5 Hz, 4H). 1.43 (qt, J = 9.8, 4.1 Hz, 1H), 0.73 (qt, J = 8.6, 5.0 Hz, 1H), 0.56 (d, J = 7.6 Hz, 2H), 0.20 (d, J = 5.0 Hz, 2H). 13C NMR (151 MHz, cdcl3) δ 195.78, 148.73, 136.77, 119.39, 112.98, 36.88, 15.80, 3.52.	1.702	N/A - 0.14950	N/A - 11.4	>160	<0.001	>160	0.5 - 1
84		403 - 1.418 - 95	^{1}H NMR (500 MHz, cdcl3) δ 16.34 (s, 1H). 8.25 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 3.14 (s, 3H), 2.93 (dd, J = 18.2, 4.6 Hz, 1H), 2.73 (dd, J = 18.5, 10.1 Hz, 1H), 2.60 – 2.46 (m, 1H), 2.33 (dd, J = 16.6, 11.1 Hz, 1H), 1.47 – 1.32 (m, 1H), 0.71 (td, J = 8.7, 4.7 Hz, 1H). 0.60 – 0.51 (m, 2H), 0.17 (p, J = 6.2 Hz, 2H).	>100	N/A - 0.1495	N/A - >669	>160	0.00478 4	>160	0 - 0.5
85		344 - 1.405 - 91	^{1}H NMR (500 MHz, cdcl3) δ 16.83 (s, 1H). 8.45 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 2.88 – 2.82 (m, 2H), 2.54 – 2.48 (m, 2H), 1.96 (p, J = 6.8 Hz, 2H), 1.88 (q, J = 6.6 Hz, 2H).	0.04924	N/A - 0.01883	N/A - 2.6	10.2	0.00069 17	>160	0 - 0.5
86		370 - 1.543 - 95	^{1}H NMR (500 MHz, cdcl3) δ 16.55 (d, J = 362.0 Hz, 1H), 8.48 (d, J = 10.7 Hz, 1H), 7.95 (dd, J = 15.0, 8.0 Hz, 1H), 7.37 (t, J = 8.1 Hz, 1H), 2.80 (t, J = 6.4 Hz, 1H), 2.72 (dt, J = 11.3, 8.7 Hz, 1H), 2.38 – 2.24 (m, 2H), 2.15 (dd, J = 13.8, 7.7 Hz, 2H), 2.11 (d, J = 6.4 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.92 – 1.80 (m, 1H). 1.76 (d, J = 7.3 Hz, 1H)	16.13	N/A - 0.02486	N/A - 648.8	>160	0.00154	>160	0 - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
87		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
88		TBD - TBD - TBD	TBD	1.313	0.297 - 0.08046	4.4 - 16.3	51.3	0.0015	160	0 - 0.5
89		396.80 - 1.20 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.68 (s, 6H), 4.29 (s, 2H), 7.40 (d, J=7.95 Hz, 1H), 7.65 (m, 2H)	73.96	N/A - 0.03564	N/A - 2075.2	>160	0.00362 2	>160	1 - 1
90		377.00 - 1.67 - 91	1H NMR(DMSO-d6, 500 MHz): δ (ppm) 1.38 (s, 12H), 7.59 (d, J=8.02 Hz, 1H), 7.79 (d, J=8.03 Hz, 1H), 7.91 (s, 1H)	100	N/A - 0.07703	N/A - 1298.2	>160	0.00676	>160	0 - 0
91		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
92		370.2 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 8.60 (d, J = 2.0 Hz, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.12 (s, 1H), 5.32 (p, J = 6.7 Hz, 1H), 1.61 (d, J = 6.7 Hz, 6H), 1.54 (s, 6H), 1.51 (s, 6H).	>160	N/A - 0.65580	N/A - >152	>160	2.338	>160	0 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
93		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
94		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
95		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
96		359.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 16.31 (s, 1H), 8.44 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 3.77 – 2.72 (m, 4H), 2.63 – 1.83 (m, 2H), 1.34 – 0.99 (m, 3H).	100	N/A - 0.05178	N/A - 1931.2	>160	0.00509	>160	0 - 0
97		413.2 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 16.35 (s, 1H), 8.47 (d, J = 16.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 15.4, 7.9 Hz, 1H), 3.92 (t, J = 10.5 Hz, 2H), 3.67 (dt, J = 32.3, 6.7 Hz, 2H), 2.76 (dt, J = 157.2, 6.7 Hz, 2H).	>100	N/A - 0.09513	N/A - >1051	>160	0.01028	>160	TBD - TBD
98		371.0 - TBD - TBD	1H NMR (400 MHz, CDCl3) δ 17.25 (d, J = 713.2 Hz, 1H), 8.46 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 7.7, 3.3 Hz, 1H), 3.55 (dt, J = 33.2, 6.8 Hz, 2H), 2.94 – 2.73 (m, 1H), 2.48 (t, J = 6.9 Hz, 2H), 1.08 – 0.55 (m, 4H).	100	N/A - 0.16470	N/A - 607.2	14.31	0.0117	160	TBD - TBD

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		Poppy - Grass
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	
99		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
100		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
101		387.0 - TBD - TBD	^{1}H NMR (500 MHz, cdcl3) δ 16.37 (s, 1H), 8.47 (s, 1H), 7.95 (t, J = 7.7 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 4.35 – 4.07 (m, 1H), 4.01 – 3.73 (m, 2H), 3.73 – 3.37 (m, 2H), 3.29 (dt, J = 27.9, 11.0 Hz, 1H), 3.20 – 3.11 (m, 1H), 2.80 – 2.60 (m, 1H), 2.44 – 2.27 (m, 1H).	>100	N/A - 0.05472	N/A - >1827	>160	0.00335 6	>160	TBD - TBD
102		425.0 - TBD - TBD	^{1}H NMR (500 MHz, cdcl3) δ 16.41 (s, 1H), 8.47 (d, J = 15.0 Hz, 1H), 7.94 (t, J = 8.6 Hz, 1H), 7.76 (d, J = 98.4 Hz, 1H), 7.62 – 7.31 (m, 2H), 4.22 (q, J = 7.3 Hz, 1H), 4.06 (q, J = 7.3 Hz, 1H), 3.95 (t, J = 6.9 Hz, 1H), 3.88 (t, J = 6.8 Hz, 1H), 2.99 (t, J = 6.8 Hz, 1H), 2.68 (t, J = 6.8 Hz, 1H), 1.54 – 1.37 (m, 3H).	>100	N/A - 0.04293	N/A - >2329.4	>160	0.00410 7	>160	0 - 0
103		428 - 1.324 - 95	^{1}H NMR (500 MHz, dmso) δ 17.61 (s, 1H), 7.75 – 7.45 (m, 4H), 7.28 (d, J = 57.2 Hz, 3H), 3.91 (s, 2H), 3.63 (s, 3H), 3.05 (s, 1H), 2.68 (s, 1H).	>100	N/A - 0.99620	N/A - >100	>160	18.53	>160	1 - 1
104		395.2 - 1.32 - 90	^{1}H NMR (500 MHz, cdcl3) δ 16.86 (s, 1H), 7.94 (d, J = 15.6 Hz, 1H), 7.91 – 7.80 (m, 2H), 7.33 (dd, J = 8.9, 4.6 Hz, 1H), 7.19 (t, J = 8.2 Hz, 2H), 7.03 (t, J = 8.4 Hz, 1H), 3.97 (dt, J = 19.6, 6.6 Hz, 2H), 3.18 (dd, J = 20.5, 1.2 Hz, 3H), 2.99 – 2.74 (m, 2H).	17.79	N/A - 0.40210	N/A - 44.2	>160	1.169	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
105		469.2 - TBD - TBD	^{1}H NMR (500 MHz, cdcl3) δ 17.66 (d, J = 309.4 Hz, 1H), 8.00 (dd, J = 26.4, 8.3 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.36 (dd, J = 8.6, 4.8 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.16 – 7.08 (m, 1H), 7.00 (t, J = 8.5 Hz, 1H), 3.99 (d, J = 23.2 Hz, 3H), 3.93 (t, J = 6.7 Hz, 2H), 3.77 – 3.71 (m, 1H), 2.87 (s, 3H), 2.75 (d, J = 6.8 Hz, 1H).	26.97	N/A - 0.85860	N/A - 31.4	>160	0.03217	>160	0.5 - 0
106		460.2 - 1.441 - 91	^{1}H NMR (600 MHz, cdcl3) δ 17.58 (d, J = 599.1 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.33 – 7.27 (m, 1H), 7.27 – 7.21 (m, 1H), 7.17 (t, J = 8.5 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.71 (dd, J = 45.3, 8.2 Hz, 1H), 3.99 (t, J = 6.3 Hz, 1H), 3.93 (t, J = 6.6 Hz, 1H), 3.89 – 3.77 (m, 4H), 2.91 (t, J = 6.3 Hz, 1H), 2.78 (t, J = 6.6 Hz, 1H), 1.44 (dt, J = 35.4, 7.2 Hz, 6H).	100	N/A - 0.94380	N/A - 106.0	>160	3.577	>160	1 - 1
107		TBD - TBD - TBD	TBD	TBD	N/A - TBD	N/A - TBD	TBD	TBD	TBD	TBD - TBD
108		386 - 1.493 - 91	^{1}H NMR (600 MHz, cdcl3) δ 17.70 (d, J = 681.0 Hz, 1H), 8.00 (d, J = 121.4 Hz, 1H), 7.64 (dd, J = 54.1, 2.1 Hz, 1H), 7.49 (t, J = 9.6 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.31 (qd, J = 6.8, 4.3 Hz, 2H), 7.17 (t, J = 8.4 Hz, 1H), 7.11 (t, J = 8.3 Hz, 1H), 3.96 (q, J = 6.8 Hz, 2H), 2.91 (dt, J = 32.3, 6.5 Hz, 2H).	96.8	N/A - 22.67600	N/A - 4.3	>160	>160	>160	1 - 1
109		397 - 1.454 - 91	^{1}H NMR (600 MHz, cdcl3) δ 18.29 (s, 1H), 8.62 (d, J = 49.8 Hz, 1H), 8.35 (s, 1H), 8.10 (d, J = 104.4 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.32 (s, 2H), 7.15 (d, J = 36.5 Hz, 2H), 3.98 (t, J = 6.6 Hz, 2H), 2.97 (s, 1H), 2.91 (s, 1H).	68.0	N/A - >100	N/A - N/A	>160	>160	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
110		396 - 1.037 - 91	^{1}H NMR (500 MHz, dmso) δ 12.99 (s, 1H), 12.10 (s, 1H), 11.97 (s, 1H), 7.47 (s, 1H), 7.36 (s, 2H), 7.21 (s, 2H), 7.12 (d, J = 8.3 Hz, 1H), 3.89 (t, J = 6.6 Hz, 2H), 3.15 (d, J = 5.6 Hz, 1H), 2.80 (s, 2H).	31.45	N/A - >100	N/A - N/A	>160	>160	>160	1 - 1
111		425 - 1.523 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.48 (d, J = 709.8 Hz, 1H), 8.06 (s, 1H), 7.90 – 7.80 (m, 2H), 7.33 (dd, J = 8.5, 4.8 Hz, 1H), 7.19 (t, J = 8.2 Hz, 2H), 7.06 (t, J = 8.1 Hz, 1H), 3.98 (dt, J = 13.4, 6.7 Hz, 2H), 2.90 (dt, J = 105.0, 6.5 Hz, 2H).	47.22	N/A - 0.04799	N/A - 984.0	>160	0.1693	38.22	1 - 1
112		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
113		425.2 - 1.509 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.30 (d, J = 845.7 Hz, 1H), 8.28 (dd, J = 46.0, 8.6 Hz, 1H), 7.81 (ddd, J = 43.0, 8.5, 2.0 Hz, 1H), 7.61 (dd, J = 24.1, 2.0 Hz, 1H), 7.34 (ddt, J = 8.1, 5.6, 2.8 Hz, 1H), 7.20 (t, J = 8.5 Hz, 1H), 7.13 – 7.06 (m, 1H), 7.00 (t, J = 8.6 Hz, 1H), 3.90 (dt, J = 24.8, 6.7 Hz, 2H), 2.85 (dt, J = 156.4, 6.7 Hz, 2H).	>160	N/A - 0.44830	N/A - >223	>160	2.501	>160	1 - 1
114		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
115		TBD - TBD - TBD	TBD	1.727	N/A - >100	N/A - N/A	>160	>160	45.09	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
116		398 - 1.416 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.68 (s, 1H), 8.05 (d, J = 62.5 Hz, 1H), 7.30 (dd, J = 8.7, 4.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.16 (t, J = 8.5 Hz, 1H), 7.09 (t, J = 8.5 Hz, 1H), 4.26 (q, J = 7.4 Hz, 1H), 4.16 (q, J = 7.3 Hz, 1H), 3.88 (t, J = 6.4 Hz, 2H), 2.91 (t, J = 6.4 Hz, 1H), 2.79 (t, J = 6.6 Hz, 1H), 1.56 (t, J = 7.3 Hz, 3H).	25.06	N/A - 0.05651	N/A - 443.5	>160	1.783	>160	0.5 - 1
117		TBD - TBD - TBD	TBD	>100	N/A - >100	N/A - N/A	>160	>160	>160	1 - 1
118		420.2 - 3.087 - 95	^{1}H NMR (500 MHz, dmso) δ 12.25 (s, 1H), 8.91 (d, J = 7.0 Hz, 1H), 7.67 (s, 1H), 7.53 (d, J = 38.5 Hz, 2H), 7.25 (t, J = 7.0 Hz, 4H), 3.94 (s, 2H), 2.81 (d, J = 48.1 Hz, 2H).	>100	N/A - 2.98860	N/A - >33	>160	0.00949 4	>160	1 - 1
119		TBD - TBD - TBD	TBD	>100	N/A - >100	N/A - N/A	>160	>160	>160	1 - 1
120		400.0 - TBD - TBD	TBD	7.776	N/A - 20.85	N/A - 0.4	>160	>160	>160	TBD - TBD

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
121		386 - 1.417 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.32 (d, J = 457.2 Hz, 1H), 7.44 (dd, J = 45.7, 5.2 Hz, 1H), 7.33 (ddt, J = 8.3, 6.0, 2.7 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.10 – 6.99 (m, 2H), 3.90 (t, J = 6.6 Hz, 2H), 2.85 (dt, J = 102.2, 6.5 Hz, 2H).	35.17	N/A - 0.24470	N/A - 143.7	>160	2.034	>160	1 - 1
122		387 - 1.409 - 91	^{1}H NMR (500 MHz, dmso) δ 13.30 (s, 1H), 8.64 (s, 1H), 7.39 (m, 2H), 7.25 (d, J = 14.4 Hz, 2H), 3.89 (t, J = 6.6 Hz, 2H), 2.82 (s, 2H).	>100	N/A - 0.40610	N/A - >246	>160	4.626	>160	1 - 1
123		370 - 1.403 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.37 (d, J = 424.5 Hz, 1H), 7.49 (d, J = 44.8 Hz, 1H), 7.32 (dd, J = 8.7, 4.7 Hz, 1H), 7.23 – 7.11 (m, 2H), 7.06 (t, J = 8.6 Hz, 1H), 6.58 (d, J = 18.2 Hz, 1H), 3.90 (t, J = 6.6 Hz, 2H), 2.86 (dt, J = 82.7, 6.5 Hz, 2H).	>100	N/A - 0.44640	N/A - >224	>160	1.441	>160	1 - 1
124		458 - 1.521 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.40 (d, J = 727.3 Hz, 1H), 8.26 (d, J = 67.9 Hz, 1H), 7.89 (dd, J = 37.8, 8.1 Hz, 1H), 7.47 (dd, J = 30.7, 8.0 Hz, 1H), 7.35 (dd, J = 8.9, 4.6 Hz, 1H), 7.19 (t, J = 8.5 Hz, 1H), 7.13 (dd, J = 8.7, 4.9 Hz, 1H), 7.02 (q, J = 8.9 Hz, 1H), 3.91 (q, J = 10.7 Hz, 2H), 3.17 (d, J = 13.6 Hz, 3H), 3.01 (t, J = 6.6 Hz, 1H), 2.73 (d, J = 40.9 Hz, 1H).	>100	N/A - 0.52520	N/A - >190	>160	0.0049	>160	0.5 - 0.5
125		414 - 1.57 - 91	^{1}H NMR (500 MHz, cdcl3) δ 17.33 (d, J = 541.2 Hz, 1H), 7.73 – 7.50 (m, 2H), 7.41 (dd, J = 29.1, 8.0 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.22 – 7.15 (m, 2H), 7.13 – 7.01 (m, 1H), 3.92 (d, J = 8.5 Hz, 2H), 2.95 (dt, J = 31.5, 6.7 Hz, 1H), 2.76 (s, 1H).	>100	N/A - 0.17340	N/A - >577	>160	0.0236	>160	0 - 0.5

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
126		448.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 17.66 (d, J = 309.4 Hz, 1H), 8.00 (dd, J = 26.4, 8.3 Hz, 1H), 7.65 (t, J = 7.2 Hz. 1H), 7.36 (dd, J = 8.6, 4.8 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.16 – 7.08 (m, 1H), 7.00 (t, J = 8.5 Hz, 1H), 3.99 (d, J = 23.2 Hz, 3H), 3.93 (t, J = 6.7 Hz, 2H), 3.77 – 3.71 (m. 1H), 2.87 (s, 3H), 2.75 (d, J = 6.8 Hz, 1H).	>100	N/A - 0.07630	N/A - >1311	17.01	0.001779	34.92	NG - 1
127		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
128		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
129		395.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 17.29 (s, 1H), 8.72 (dd, J = 8.0, 2.0 Hz, 1H), 8.36 (d, J = 2.0 Hz, 1H), 8.08 (d, J = 15.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.26 – 7.14 (m, 2H), 7.05 (t, J = 8.6 Hz, 1H), 5.30 (dp, J = 32.4, 6.7 Hz, 1H), 3.98 (dt, J = 26.3, 6.6 Hz, 2H), 2.95 (t, J = 6.4 Hz, 1H), 2.80 (t, J = 6.6 Hz, 1H), 1.64 – 1.55 (m, 6H).	>100	N/A - 0.65410	N/A - >152.9	>160	100	>160	1 - - 1
130		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
131		409.2 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 7.95 (d, J = 18.7 Hz, 1H), 7.88 (d, J = 12.8 Hz, 1H), 7.35 (dd, J = 8.7, 4.9 Hz, 1H), 7.20 – 6.98 (m, 3H), 5.45 – 5.16 (m, 1H), 3.93 (dt, J = 13.4, 6.5 Hz, 2H), 2.87 (dt, J = 114.5, 6.5 Hz, 2H), 2.65 (d, J = 7.4 Hz, 3H), 1.60 – 1.58 (m, 3H), 1.55 – 1.53 (m, 3H).	100	N/A - 0.55460	N/A - 180.3	>160	0.1053	>160	0 - - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		Poppy - Grass
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	
132		377.20 - 4.37 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 1.31 (m, 6H), 1.46 (s, 6H), 7.43 (m, 1H), 7.63 (m, 1H), 7.68 (m, 1H), 16.18 (s, 1H)	51.8	N/A - 0.25750	N/A - 201.2	>160	0.01345	>160	0 - 0
133		411.00 - 1.16 - 91	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 3.09 (m, 1H), 4.34 (m, 2H), 7.02 (m, 1H), 7.15 (t, J=8.35 Hz, 1H), 7.46 (m, 1H), 7.62 (m, 1H), 7.75 (m, 1H), 8.03 (d, J=8.02 Hz, 1H), 8.49 (m, 1H)	43.5	N/A - 0.03228	N/A - 1347.6	>160	0.07015	>160	1 - 1
134		382.00 - 1.14 - 90	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 4.35 (m, 2H), 7.27 (m, 1H), 7.41 (m, 2H), 7.62 (m, 2H), 7.68 (m, 2H), 7.77 (m, 1H)	100	N/A - 0.01117	N/A - 8952.6	>160	0.1077	>160	1 - 1
135		417 - 1.452 - 98	TBD	25	N/A - 0.00863	N/A - 2895.5	>30	0.07602	60.34	1 - 1
136		400.00 - 1.25 - 85	1H NMR(Chloroform-d, 500 MHz): δ (ppm) 4.33 (m, 2H), 7.10 (m, 2H), 7.59 (m, 2H), 7.66 (m, 2H), 7.77 (m, 1H)	29.08	N/A - 0.04485	N/A - 648.4	>160	10.04	>160	1 - 1
137		TBD - TBD - TBD	TBD	TBD	TBD - TBD	TBD - TBD	TBD	TBD	TBD	TBD - TBD
138		379 - 1.319 - 91	1H NMR (500 MHz, dmso) δ 12.86 (s, 1H), 8.55 (s, 1H), 8.32 (s, 1H), 8.12 (s, 1H), 7.93 (s, 2H), 7.60 (d, J = 8.1 Hz, 3H).	23.9	N/A - 6.47760	N/A - 3.7	13.17	>100	144	NG - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
139		413 - 1.442 - 91	^{1}H NMR (500 MHz, dmso) δ 12.90 (s, 1H), 8.54 (s, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.93 (s, 2H), 7.67 (d, J = 8.2 Hz, 2H).	>100	N/A - >100	N/A - N/A	32.39	>100	>160	NG - 1
140		413 - 1.399 - 91	^{1}H NMR (500 MHz, dmso) δ 12.93 (s, 1H), 8.54 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.88 (s, 2H), 7.70 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H).	>100	N/A - 4.725	N/A - >21	>160	>100	>160	NG - 1
141		397 - 1.359 - 95	^{1}H NMR (500 MHz, dmso) δ 12.18 (s, 1H), 8.50 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.76 (ddd, J = 9.6, 4.9, 2.7 Hz, 2H), 7.51 – 7.44 (m, 2H).	>100	N/A - 0.01432	N/A - >6983	32.39	0.00734 2	>160	0 - 1
142		397 - 1.359 - 91	^{1}H NMR (500 MHz, TFA) δ 8.63 (s, 1H), 8.19 (s, 1H), 7.91 (s, 1H), 7.67 (s, 2H), 7.36 (s, 2H).	114.5	N/A - 0.04512	N/A - 2537.7	41.2	0.0173	59.57	1 - 1
143		378.2 - 1.311 - 95	^{1}H NMR (500 MHz, dmso) δ 14.05 (s, 1H), 8.80 (s, 1H), 8.27 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.55 (tt, J = 10.1, 2.9 Hz, 2H), 7.49 (td, J = 6.7, 2.9 Hz, 1H), 3.28 (s, 1H).	>100	N/A - 0.11230	N/A - >890	>50	0.0123	~100	0 - 1
144		377 - 1.392 - 95	^{1}H NMR (500 MHz, dmso) δ 12.63 (s, 1H), 8.21 (s, 1H), 8.03 (q, J = 8.1 Hz, 2H), 7.62 (d, J = 7.8 Hz, 2H), 7.51 (t, J = 7.7 Hz, 2H), 7.41 (dd, J = 8.3, 5.2 Hz, 2H), 7.06 (d, J = 2.5 Hz, 1H).	90.74	N/A - 0.79220	N/A - 114.5	TBD	3.52	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	Poppy - Grass
145		386 - 1.39 - 91	^{1}H NMR (500 MHz, dmso) δ 12.04 (s, 1H), 8.03 – 7.99 (m, 1H), 7.87 – 7.81 (m, 1H), 7.80 – 7.71 (m, 3H), 7.52 – 7.43 (m, 2H).	>100	N/A - 0.00970	N/A - >10309	43.76	<0.001	37.25	NG - 0.5
146		397.2 - 1.364 - 91	^{1}H NMR (500 MHz, dmso) δ 12.30 (s, 1H), 8.59 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.41 (t, J = 8.8 Hz, 2H).	2.608	N/A - 0.01011	N/A - 258.0	4.229	0.1753	50.19	NG - 1
147		430 - 1.258 - 91	^{1}H NMR (500 MHz, dmso) δ 12.29 (s, 1H), 8.62 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.74 (dt, J = 8.5, 4.3 Hz, 2H), 7.42 (t, J = 8.6 Hz, 2H), 3.34 (s, 3H).	>100	N/A - 0.04178	N/A - >2393	>160	0.1397	>160	1 - 1
148		386 - 1.422 - 95	^{1}H NMR (500 MHz, dmso) δ 12.11 (s, 1H), 8.19 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.42 (t, J = 8.7 Hz, 2H).	100	N/A - 0.01002	N/A - 9980.0	6.542	8.189	252.7	NG - 1
149		380 - 1.323 - 91	^{1}H NMR (500 MHz, dmso) δ 12.43 (s, 1H), 8.64 (d, J = 4.9 Hz, 1H), 8.53 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.17 (td, J = 7.8, 1.9 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.62 (dd, J = 7.6, 4.8 Hz, 1H).	24.63	N/A - 0.05446	N/A - 452.3	>160	<0.001	65.71	0 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		Poppy - Grass
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	
150		380 - 1.175 - 91	^{1}H NMR (500 MHz, dmso) δ 12.35 (s, 1H), 8.93 (d, J = 2.6 Hz, 1H), 8.77 (dd, J = 4.9, 1.5 Hz, 1H), 8.50 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.19 (dt, J = 8.3, 2.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 8.2, 4.8 Hz, 1H).	27.41	N/A - 0.00902	N/A - 3037.8	>160	0.02671	>160	1 - 1
151		411 - 1.377 - 91	^{1}H NMR (500 MHz, dmso) δ 12.14 (s, 1H), 8.58 (s, 1H), 8.37 (s, 1H), 8.09 (s, 1H), 7.40 (dd, J = 8.5, 5.3 Hz, 2H), 7.25 (dd, J = 10.0, 7.6 Hz, 2H), 5.62 (s, 2H).	100	N/A - 0.01483	N/A - 6743.1	>160	0.00680 9	42.91	0 - 0
152		331 - 1.14 - 95	^{1}H NMR (500 MHz, dmso) δ 12.01 (s, 1H), 8.55 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).	>100	N/A - 0.01236	N/A - >8091	>160	<0.001	36.15	0 - 1
153		343 - 1.149 - 95	^{1}H NMR (500 MHz, dmso) δ 12.12 (s, 1H), 8.57 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 3.72 (p, J = 5.5 Hz, 1H), 1.18 (d, J = 5.6 Hz, 4H).	>100	N/A - 0.01524	N/A - >6562	>160	0.00269 8	>160	0 - 0.5
154		359.2 - 1.263 - 91	TBD	>100	N/A - 0.01283	N/A - >7794	100	0.00226 9	9.724	0 - 0

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*		Poppy - Grass
				SPR IC_{50} [μM]	HPD IC_{50} [μM]	Selectivity	SPR IC_{50} [μM]	HPD IC_{50} [μM]	LD_{50} [μM]	
155		393 - 1.363 - 93	^{1}H NMR (500 MHz, dmso) δ 12.07 (s, 1H), 8.48 (s, 1H), 8.26 (dd, J = 8.1, 1.8 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.46 (dd, J = 7.9, 1.4 Hz, 1H), 7.44 – 7.37 (m, 1H), 2.09 (s, 3H).	88.46	N/A - 0.09755	N/A - 906.8	160	0.1635	>160	0 - 1
156		386.2 - TBD - TBD	1H NMR (500 MHz, dmso) δ 8.53 (s, 2H), 8.15 (s, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 4.44 (s, 1H), 3.45 (d, J = 13.6 Hz, 2H), 3.04 (dt, J = 12.3, 6.2 Hz, 2H), 2.11 (dq, J = 15.0, 7.6 Hz, 4H).	100	N/A - 0.89780	N/A - 111.4	>160	0.927	>160	0.5 - 1
157		372.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 8.53 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 3.48 (s, 3H), 3.19 (s, 3H).	98.31	N/A - 0.01838	N/A - 5348.7	>160	0.07169	>160	0.5 - 0.5
158		437.0 - TBD - TBD	1H NMR (500 MHz, dmso) δ 8.33 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 7.6 Hz, 2H), 3.06 (s, 3H).	>100	N/A - 0.485	N/A - >206	>160	2.873	>160	TBD - TBD
159		393 - 1.266 - 90	^{1}H NMR (600 MHz, cdcl3) δ 8.51 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.36 (dd, J = 8.5, 5.2 Hz, 2H), 7.08 (t, J = 8.6 Hz, 2H), 3.99 (s, 2H).	17.66	N/A - 0.01885	N/A - 936.9	>160	0.05613	>160	1 - 1
160		393 - 1.336 - 93	^{1}H NMR (500 MHz, dmso) δ 8.01 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 7.2 Hz, 2H), 7.05 (dd, J = 9.8, 7.6 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 1H).	35.09	N/A - 0.01175	N/A - 2986.4	143.9	1.945	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
161		382.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 17.32 (s, 1H), 8.07 (s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.36 (s, 1H), 7.08 (t, J = 8.5 Hz, 2H), 4.08 (s, 2H).	3.284	N/A - 0.01664	N/A - 197.4	24.27	2.99	38.25	TBD - TBD
162		426.2 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 8.84 (s, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 6.9 Hz, 2H), 7.08 (t, J = 8.5 Hz, 2H), 4.09 (s, 2H), 3.23 (d, J = 1.5 Hz, 3H).	22.73	N/A - 0.01533	N/A - 1482.7	>160	0.1143	>160	1 - 1
163		379 - 1.185 - 91	^{1}H NMR (500 MHz, dmso) δ 8.36 (d, *J* = 1.8 Hz, 1H), 8.04 – 7.99 (m, 1H), 7.63 – 7.55 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.10 (m, 2H), 6.90 (s, 1H).	94.1	N/A - 0.01472	N/A - 6392.7	>160	0.777	>160	1 - 1
164		409.0 - TBD - TBD	1H NMR (500 MHz, cdcl3) δ 8.51 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.26 (s, 1H), 3.99 (s, 2H).	14.57	N/A - 0.02060	N/A - 707.3	>160	0.3408	>160	1 - 1
165		381 - 1.416 - 95	^{1}H NMR (500 MHz, dmso) δ 8.30 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 4.50 (s, 1H), 2.30 (d, *J* = 6.7 Hz, 2H). 1.59 (t, *J* = 13.0 Hz, 6H), 1.12 (h, *J* = 13.3 Hz, 3H), 0.87 (q, *J* = 11.5 Hz, 2H).	19.23	N/A - 0.02471	N/A - 778.2	>160	0.03899	>160	1 - 1

Cmpd. No.	Structure	MS-ESI (m/z) - RT, min - Purity	NMR	*In Vitro*			*In Vivo*			
				SPR IC_{50} [µM]	HPD IC_{50} [µM]	Selectivity	SPR IC_{50} [µM]	HPD IC_{50} [µM]	LD_{50} [µM]	Poppy - Grass
166		392 - 1.31 - 91	^{1}H NMR (600 MHz, dmso) δ 8.41 (s, 1H), 8.21 – 8.15 (m, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 2.48 (s, 3H).	>100	N/A - 100	N/A - N/A	>160	3.392	>160	1 - 1

Prophetic Biological Example 8: Evaluation of Compounds

[0624] The effect of compounds of the present disclosure on PAH-dependent tyrosine biosynthesis will be assessed in accordance with the methods described in Biological Example 1.

[0625] The effect of compounds of the present disclosure on BH4 and BH2 levels will be assessed in accordance with the methods described in Biological Example 2.

[0626] The effect of compounds of the present disclosure on SPR activity will be assessed in accordance with the methods described in Biological Example 3.

[0627] The effect of compounds of the present disclosure on neurocognitive function will be assessed in accordance with the methods described in Biological Example 4.

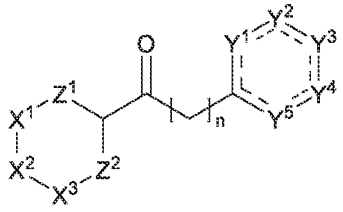
Equivalents

[0628] While the present disclosure has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present disclosure.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all === together form an aryl ring or heteroaryl ring, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond;

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$;

X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$;

X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond;

X^1 is NR^{1l} or O, X^2 is C(O), and X^3 is NR^{3l} or O; or

X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$;

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl; wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or

more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3i} and $R^{3i'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3i} or $R^{3i'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3j} and $R^{3j'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3j} or $R^{3j'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{2h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1i} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1i} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1j} and R^{2j} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1j} or R^{2j} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1k} and R^{2k} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1k} or R^{2k} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, or CN;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$, then:

Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; or

Y^1 is C(O); Y^2 is $N(R^{2b2'})$; Y^3 is $C(R^{3b2'})$; Y^4 is $C(R^{4b2'})$; and Y^5 is N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN;

$R^{2b2'}$ is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

$R^{3b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

$R^{4b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

$R^{2b2'}$ combines with $R^{3b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{4b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{4b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

$R^{3b2'}$ combines with $R^{4b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{2b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} is Cl; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl, NO_2, or SO_2-C_{1-6} alkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} is NO_2; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring

may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$; then Y^1 is $C(R^{1i2})$ or N; Y^2 is $C(R^{2i2})$ or N; Y^3 is $C(R^{3i2})$ or N; Y^4 is $C(R^{4i2})$ or N; and Y^5 is $C(R^{5i2})$ or N; wherein

R^{1i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1i2} combines with R^{2i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2i2} combines with R^{3i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3i2} combines with R^{4i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4i2} combines with R^{5i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{3i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$; then Y^1 is $C(R^{1j2})$ or N; Y^2 is $C(R^{2j2})$ or N; Y^3 is $C(R^{3j2})$ or N; Y^4 is $C(R^{4j2})$ or N; and Y^5 is $C(R^{5j2})$ or N; wherein

R^{1j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1j2} combines with R^{2j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2j2} combines with R^{3j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3j2} combines with R^{4j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4j2} combines with R^{5j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{3j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond; then Y^1 is $C(R^{1k2})$ or N; Y^2 is $C(R^{2k2})$ or N; Y^3 is $C(R^{3k2})$ or N; Y^4 is $C(R^{4k2})$ or N; and Y^5 is $C(R^{5k2})$ or N; wherein

R^{1k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1k2} combines with R^{2k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2k2} combines with R^{3k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3k2} combines with R^{4k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4k2} combines with R^{5k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{3k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{11} or O, X^2 is C(O), and X^3 is NR^{31} or O; then Y^1 is $C(R^{112})$ or N; Y^2 is $C(R^{212})$ or N; Y^3 is $C(R^{312})$ or N; Y^4 is $C(R^{412})$ or N; and Y^5 is $C(R^{512})$ or N; wherein

R^{112} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{212} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{312} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{412} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{512} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{112} combines with R^{212} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{312}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{212} combines with R^{312} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{312} combines with R^{412} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{412} combines with R^{512} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{312} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

or

if X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$; then Y^1 is $C(R^{1m2})$ or N; Y^2 is $C(R^{2m2})$ or N; Y^3 is $C(R^{3m2})$ or N; Y^4 is $C(R^{4m2})$ or N; and Y^5 is $C(R^{5m2})$ or N; wherein

R^{1m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1m2} combines with R^{2m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2m2} combines with R^{3m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3m2} combines with R^{4m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4m2} combines with R^{5m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{3m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN.

2. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; or

X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l};

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^{1a} and $R^{1a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ are each H; orR^{2a} and $R^{2a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H; or

R^{1a} and R^{3a} combine to form a cycloalkyl ring, wherein the cycloalkyl ring may be unsubstituted or substituted with one or more C_{1-6} alkyl, and $R^{1a'}$, R^{2a}, $R^{2a'}$, and $R^{3a'}$ are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3b} and $R^{3b'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, F, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{3e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{4e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{5e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2; or

R^{1e2} combines with R^{2e2} to form a heteroaryl ring, and R^{3e2}, R^{4e2}, and R^{5e2} are each H;

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l}; then Y^1 is $C(R^{1l2})$; Y^2 is $C(R^{2l2})$; Y^3 is $C(R^{3l2})$; Y^4 is $C(R^{4l2})$; and Y^5 is $C(R^{5l2})$; wherein

R^{1l2} is H, C_{1-6} haloalkyl, or NO_2;

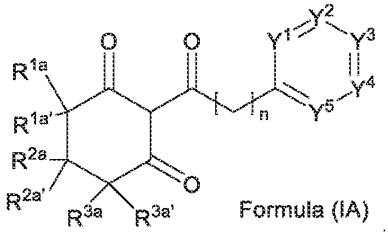
R^{2l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4l2} is H, C_{1-6} haloalkyl, or NO_2;

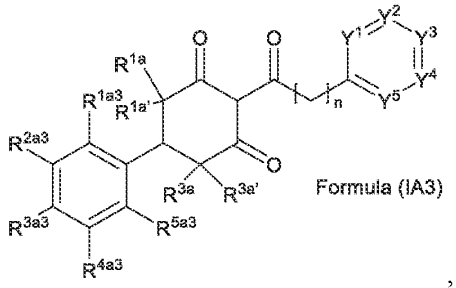
R^{5l2} is H, C_{1-6} haloalkyl, or NO_2.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IA)

4. The compound of claim 3, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

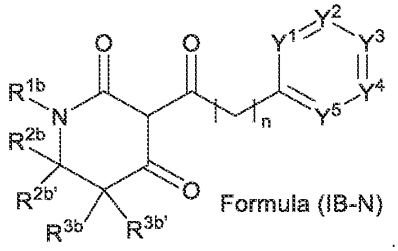


Formula (IA3)

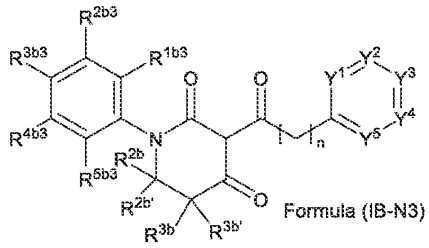
wherein R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

5. The compound of claim 4, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a3}, R^{2a3}, R^{3a3}, R^{4a3}, and R^{5a3} are each H.

6. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IB-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



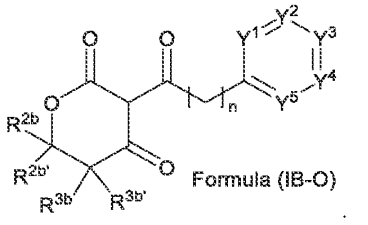
7. The compound of claim 6, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IB-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



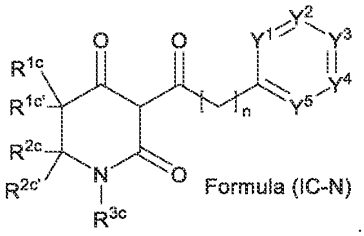
wherein R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

8. The compound of claim 7, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1b3}, R^{2b3}, R^{3b3}, R^{4b3}, and R^{5b3} are each H.

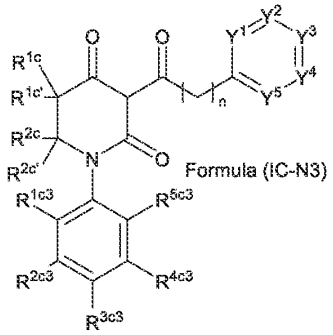
9. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



10. The compound of claim 1 or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IC-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



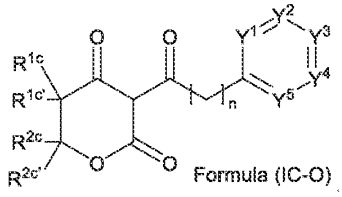
11. The compound of claim 10, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IC-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



wherein R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

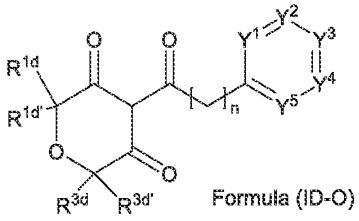
12. The compound of claim 11, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1c3}, R^{2c3}, R^{3c3}, R^{4c3}, and R^{5c3} are each H.

13. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IC-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



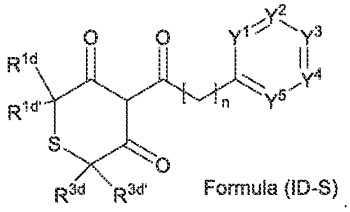
Formula (IC-O)

14. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (ID-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



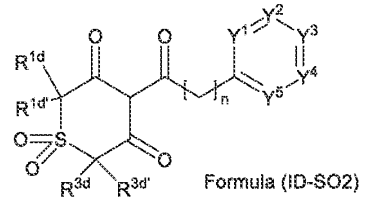
Formula (ID-O)

15. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (ID-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

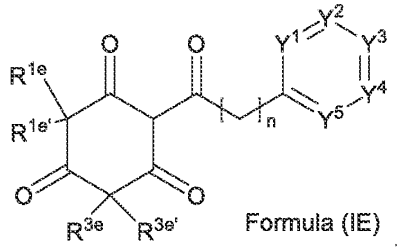


Formula (ID-S)

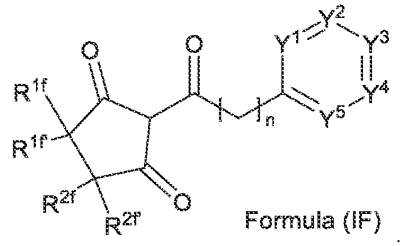
16. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (ID-SO2), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



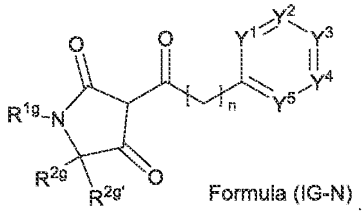
17. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



18. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IF), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

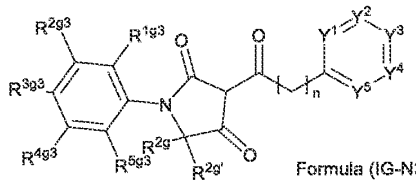


19. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IG-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IG-N)

20. The compound of claim 19, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IG-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

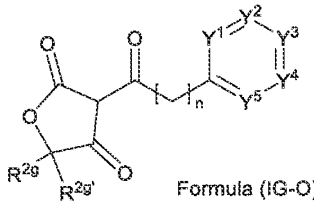


Formula (IG-N3)

wherein R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

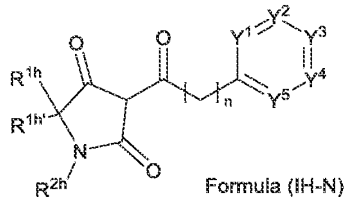
21. The compound of claim 20, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1g3}, R^{2g3}, R^{3g3}, R^{4g3}, and R^{5g3} are H.

22. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IG-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



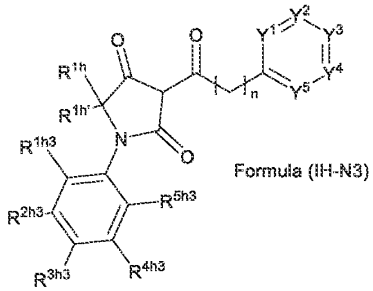
Formula (IG-O)

23. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IH-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IH-N)

24. The compound of claim 23, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IH-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

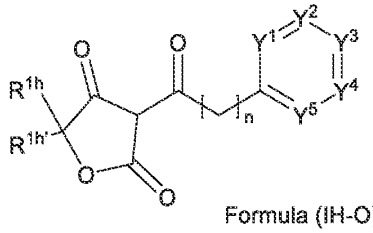


Formula (IH-N3)

wherein R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

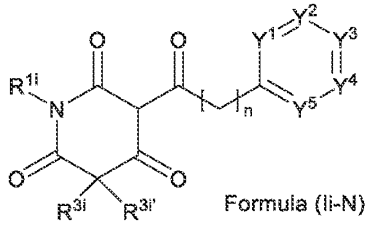
25. The compound of claim 24, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1h3}, R^{2h3}, R^{3h3}, R^{4h3}, and R^{5h3} are each H.

26. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IH-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



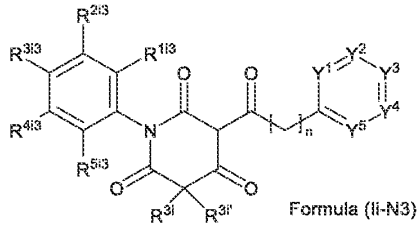
Formula (IH-O)

27. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (Ii-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (Ii-N)

28. The compound of claim 27, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (Ii-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

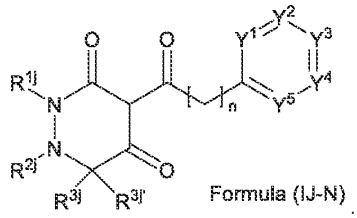


Formula (Ii-N3)

wherein R^{1i3}, R^{2i3}, R^{3i3}, R^{4i3}, and R^{5i3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

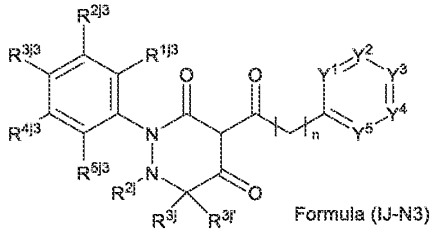
29. The compound of claim 28, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1i3}, R^{2i3}, R^{3i3}, R^{4i3}, and R^{5i3} are each H.

30. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IJ-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IJ-N)

31. The compound of claim 30, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IJ-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

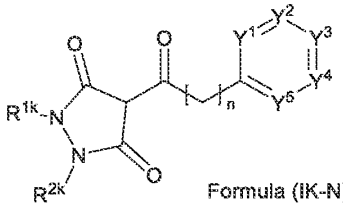


Formula (IJ-N3)

wherein R^{1j3}, R^{2j3}, R^{3j3}, R^{4j3}, and R^{5j3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

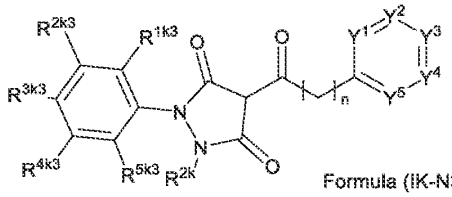
32. The compound of claim 31, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1j3}, R^{2j3}, R^{3j3}, R^{4j3}, and R^{5j3} are each H.

33. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IK-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IK-N)

34. The compound of claim 33, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IK-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

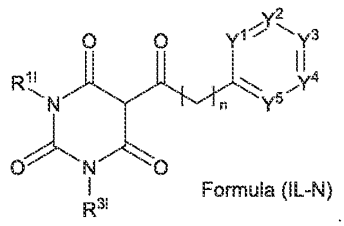


Formula (IK-N3)

wherein R^{1k3}, R^{2k3}, R^{3k3}, R^{4k3}, and R^{5k3} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

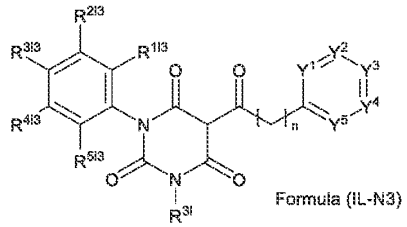
35. The compound of claim 34, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1k3}, R^{2k3}, R^{3k3}, R^{4k3}, and R^{5k3} are each H.

36. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IL-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IL-N)

37. The compound of claim 36, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IL-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

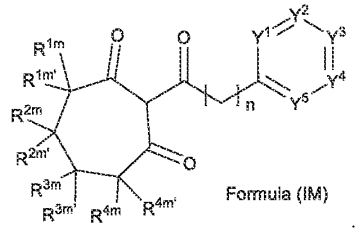


Formula (IL-N3)

wherein R^{113}, R^{213}, R^{313}, R^{413}, and R^{513} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

38. The compound of claim 37, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{113}, R^{213}, R^{313}, R^{413}, and R^{513} are each H.

39. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IM), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IM)

40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein n is 0.

41. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein n is 1.

42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein Y^1 is $C(NO_2)$.

43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein Y^3 is $C(CF_3)$.

44. The compound of any one of claims 1-5, 10-18, 23-26, and 40-43, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3.

45. The compound of any one of claims 1-5, 10-18, 23-26, and 40-43, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each H.

46. The compound of any one of claims 1-3, 6-13, 18-22, and 40-45, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each CH_3.

47. The compound of any one of claims 1-3, 6-13, 18-22, and 40-45, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$ are CH_3 and H respectively, R^{2b} and $R^{2b'}$ are CH_3 and H respectively, R^{2c} and $R^{2c'}$ are CH_3 and H respectively, R^{2f} and $R^{2f'}$ are CH_3 and H respectively, or R^{2g} and $R^{2g'}$ are CH_3 and H respectively.

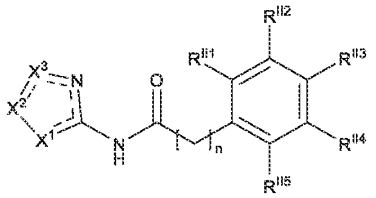
48. The compound of any one of claims 1-3, 6-13, 18-22, and 40-45, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a} and $R^{2a'}$, R^{2b} and $R^{2b'}$, R^{2c} and $R^{2c'}$, R^{2f} and $R^{2f'}$, or R^{2g} and $R^{2g'}$ are each H.

49. The compound of any one of claims 1-9, 14-17, 27-32, and 40-48, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each CH_3.

50. The compound of any one of claims 1-9, 14-17, 27-32, and 40-48, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each H.

51. The compound of any one of claims 1-2, 6, 40-43, and 46-50, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1b} is cycloalkyl or heteroaryl.

52. A compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

X^1 is NR^1, X^2 is CR^2, and X^3 is N or CH;

X^1 is O, X^2 is CR^2, and X^3 is N;

X^1 is N, X^2 is NR^1, and X^3 is N; or

X^1 is NR^3, X^2 is N, and X^3 is N;

n is 0 or 1;

R^1 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^1 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

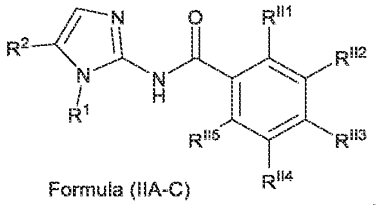
R^2 is selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, SO_2-C_{1-6} alkyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is selected from C_{4-6} alkyl, cycloalkyl, aryl substituted with one or more substituents selected from the group consisting of halo and methyl, benzyl substituted with one or more F, and heteroaryl;

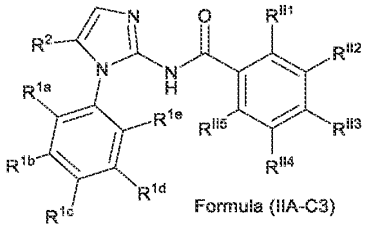
R^{II1}, R^{II2}, R^{II3}, R^{II4}, and R^{II5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

53. The compound of claim 52, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIA-C), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-C)

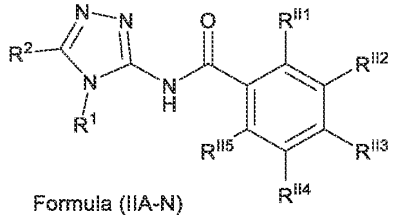
54. The compound of claim 53, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIA-C3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-C3)

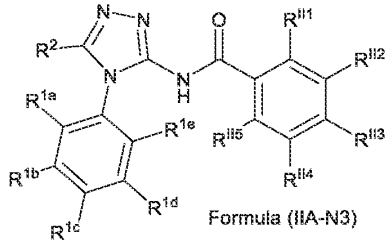
wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

55. The compound of claim 52, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIA-N), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N)

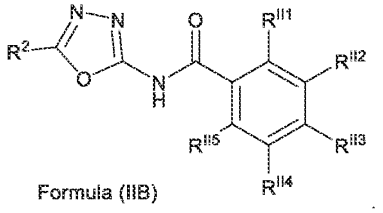
56. The compound of claim 55, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIA-N3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIA-N3)

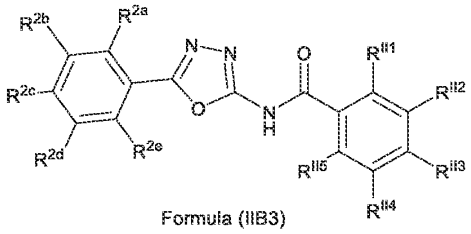
wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

57. The compound of claim 52, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIB), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIB)

58. The compound of claim 57, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIB3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

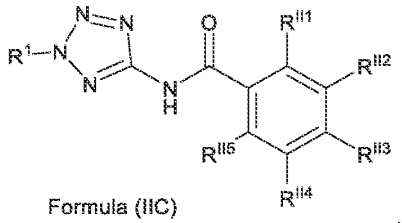


Formula (IIB3)

wherein R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

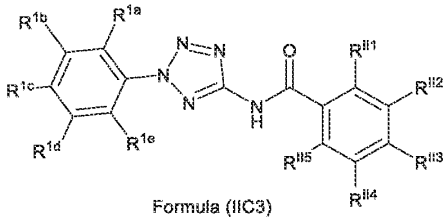
59. The compound of claim 58, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{2a}, R^{2b}, R^{2c}, R^{2d}, and R^{2e} are each H.

60. The compound of claim 52, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIC), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IIC)

61. The compound of claim 60, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IIC3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:

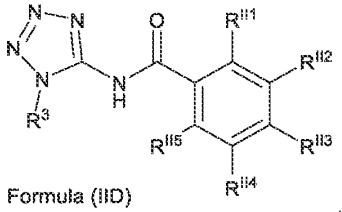


Formula (IIC3)

wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

62. The compound of any one of claims 54, 56, and 61, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, and R^{1e} are each H.

63. The compound of claim 52, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IID), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



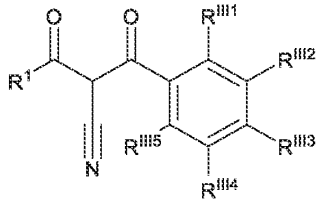
Formula (IID)

64. The compound of claim 63, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^3 is C_{4-6} alkyl or phenyl substituted with one or more halo.

65. The compound of any one of claims 52-64, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{II1} is NO_2.

66. The compound of any one of claims 52-65, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{II3} is CF_3.

67. A compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

R^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, and C_1 alkyl-heteroaryl;

wherein the C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, or C_1 alkyl-heteroaryl of R^1 is unsubstituted or substituted with halo;

R^{III1}, R^{III2}, R^{III3}, R^{III4}, and R^{III5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

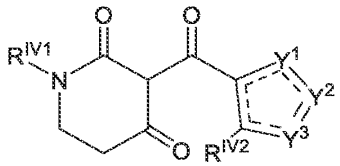
68. The compound of claim 67, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1 is aryl or C_1 alkyl-aryl, wherein the aryl or C_1 alkyl-aryl may be unsubstituted or substituted with one or more halo.

69. The compound of claim 67 or 68, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{III1} is H or NO_2.

70. The compound of any one of claims 67-69, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{III2} is H, halo, or SO_2-C_{1-6} alkyl.

71. The compound of any one of claims 67-70, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{III3} is CF_3.

72. A compound of Formula (IV):



Formula (IV)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each === independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

Y^1 is CR^1, Y^2 is N, and Y^3 is NR^3;

Y^1 is CR^1, Y^2 is O or S, and Y^3 is CR^3;

Y^1 is N, Y^2 is CR^2, and Y^3 is O or S; or

Y^1 is O or S, Y^2 is CR^2, and Y^3 is CR^3;

R^1 and R^2 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^1 or R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^3 combines with R^{IV2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

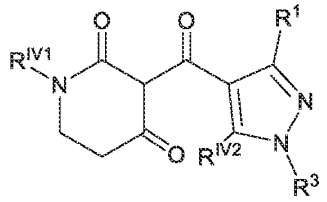
R^{IV1} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{IV1} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{IV2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

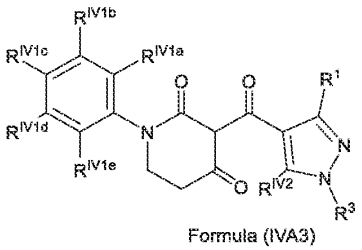
R^{IV2} combines with R^3 to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl.

73. The compound of claim 72, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVA), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVA)

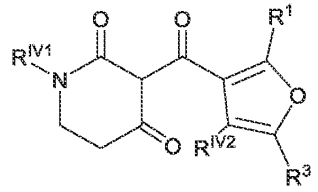
74. The compound of claim 73, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVA3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVA3)

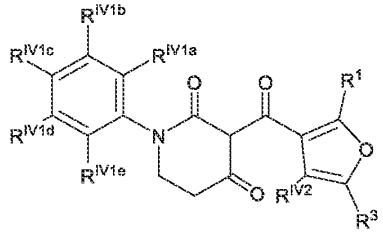
wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

75. The compound of claim 72, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVB-O), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O)

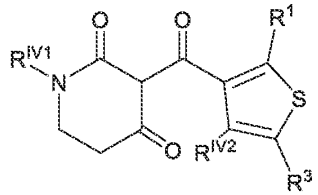
76. The compound of claim 75, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVB-O3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-O3)

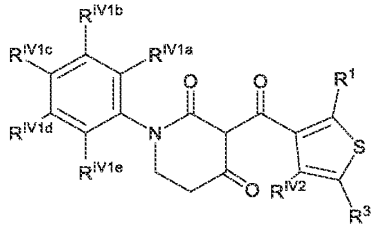
wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

77. The compound of claim 72, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVB-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S)

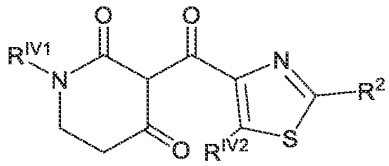
78. The compound of claim 77, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVB-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVB-S3)

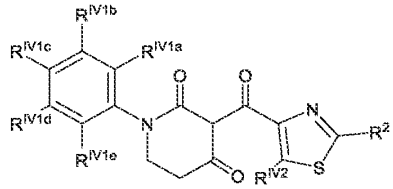
wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

79. The compound of claim 72, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVC-S), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S)

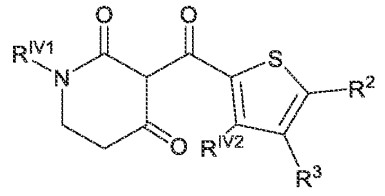
80. The compound of claim 79, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVC-S3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVC-S3)

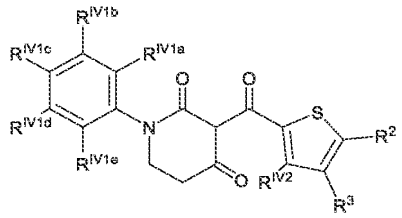
wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

81. The compound of claim 72, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVD), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD)

82. The compound of claim 81, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein the compound is of Formula (IVD3), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (IVD3)

wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and -O-C_{1-6} alkyl.

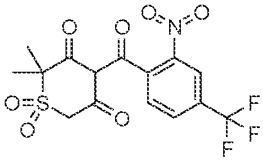
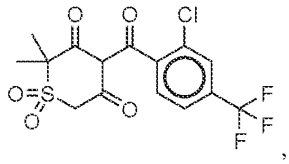
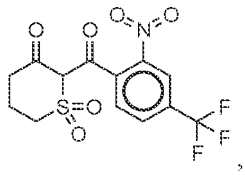
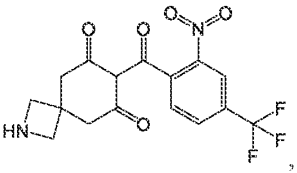
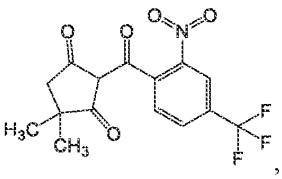
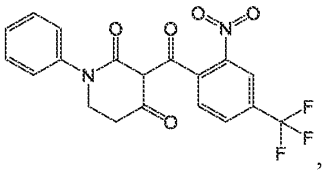
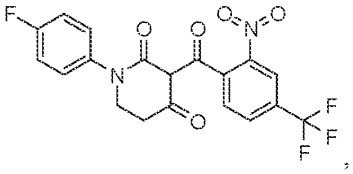
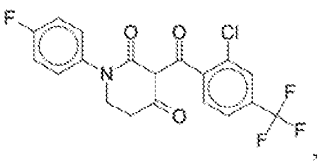
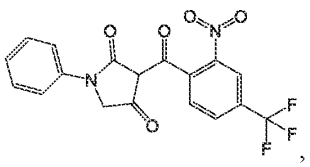
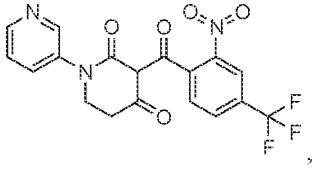
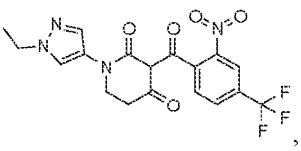
83. The compound of any one of claims 74, 76, 78, 80, or 82, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{IV1a}, R^{IV1b}, R^{IV1c}, R^{IV1d}, and R^{IV1e} are each H.

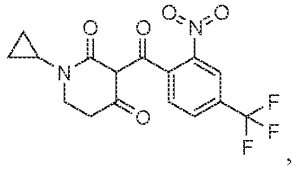
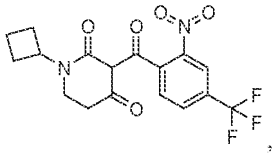
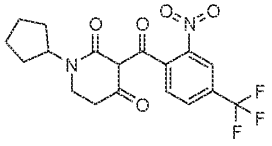
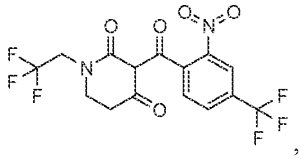
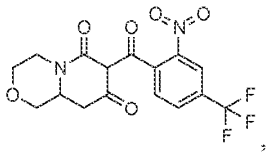
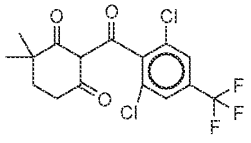
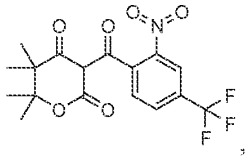
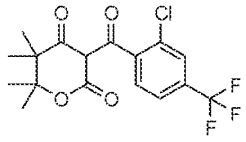
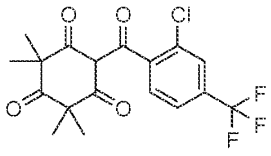
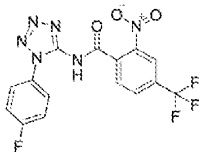
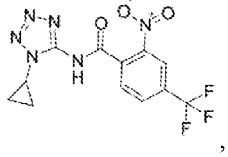
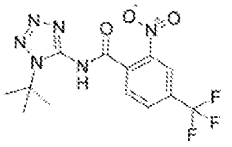
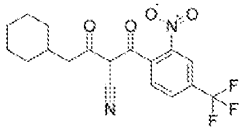
84. The compound of any one of claims 72-78 and 83, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1 is CF_3.

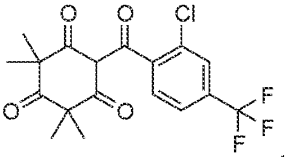
85. The compound of any one of claims 72 and 79-84, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^2 is CF_3.

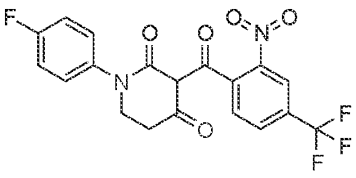
86. The compound of any one of claims 72-78 and 81-85, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^3 is C_{1-6} alkyl.

87. A compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, selected from the group consisting of the following Table 1 compounds: Compound Nos. 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 110, 111, 112, 113, 114, 116, 118, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165 and pharmaceutically acceptable salt and tautomers of any of the foregoing.

88. A compound of the structure , , , , , , , , , , .

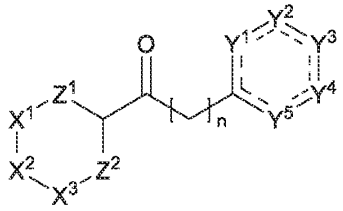
,
,
,
,
,
,
,
,
,
,
,
, or
, or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

89. A compound of the structure , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

90. A compound of the structure , or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

91. A pharmaceutical composition comprising the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

92. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (V):



Formula (V)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, or all ≡ together form an aryl ring or heteroaryl ring, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is NR^{3c} or O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond;

X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond;

X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond;

X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$;

X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$;

X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond;

X^1 is NR^{1l} or O, X^2 is C(O), and X^3 is NR^{3l} or O; or

X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$;

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{2-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl; wherein the aryl of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1c}, $R^{1c'}$, R^{2c}, or $R^{2c'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1d}, $R^{1d'}$, R^{3d}, or $R^{3d'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1e}, $R^{1e'}$, R^{3e}, or $R^{3e'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1f}, $R^{1f'}$, R^{2f}, and $R^{2f'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1f}, $R^{1f'}$, R^{2f}, or $R^{2f'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{2g} and $R^{2g'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{2g} or $R^{2g'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1h} and $R^{1h'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1h} or $R^{1h'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3i} and $R^{3i'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3i} or $R^{3i'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3j} and $R^{3j'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{3j} or $R^{3j'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

two or more of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, and $R^{4m'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1m}, $R^{1m'}$, R^{2m}, $R^{2m'}$, R^{3m}, $R^{3m'}$, R^{4m}, or $R^{4m'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{1b} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

two or more of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, and $R^{3b'}$ combine to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl, and any uncombined R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1b}, R^{2b}, $R^{2b'}$, R^{3b}, or $R^{3b'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{3c} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1c} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1g} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{2h} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{2h} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1i} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1i} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1j} and R^{2j} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1j} or R^{2j} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1k} and R^{2k} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1k} or R^{2k} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

n is 0 or 1;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$ or N; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$ or N; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3a2} is H, halo, C_{1-6} haloalkyl, NO_2, or CN;

R^{4a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5a2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1a2} combines with R^{2a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2a2} combines with R^{3a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{4a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3a2} combines with R^{4a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{5a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4a2} combines with R^{5a2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1a2}, R^{2a2}, and R^{3a2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1b} or O, X^2 is $CR^{2b}R^{2b'}$, and X^3 is $CR^{3b}R^{3b'}$, then:

Y^1 is $C(R^{1b2})$ or N; Y^2 is $C(R^{2b2})$ or N; Y^3 is $C(R^{3b2})$ or N; Y^4 is $C(R^{4b2})$ or N; and Y^5 is $C(R^{5b2})$ or N; or

Y^1 is C(O); Y^2 is N($R^{2b2'}$); Y^3 is C($R^{3b2'}$); Y^4 is C($R^{4b2'}$); and Y^5 is N; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5b2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1b2} combines with R^{2b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{3b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2b2} combines with R^{3b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{4b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3b2} combines with R^{4b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{5b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4b2} combines with R^{5b2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or OH, and R^{1b2}, R^{2b2}, and R^{3b2} are each independently selected from H, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, NO_2, and CN;

$R^{2b2'}$ is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

$R^{3b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

$R^{4b2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

$R^{2b2'}$ combines with $R^{3b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring

may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{4b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{4b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy; or

$R^{3b2'}$ combines with $R^{4b2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl or halo, and $R^{2b2'}$ is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of $R^{2b2'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O or NR^{3c}; then Y^1 is $C(R^{1c2})$ or N; Y^2 is $C(R^{2c2})$ or N; Y^3 is $C(R^{3c2})$ or N; Y^4 is $C(R^{4c2})$ or N; and Y^5 is $C(R^{5c2})$ or N; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5c2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1c2} combines with R^{2c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2c2} combines with R^{3c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{4c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3c2} combines with R^{4c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{5c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4c2} combines with R^{5c2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1c2}, R^{2c2}, and R^{3c2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$ or N; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$ or N; Y^4 is $C(R^{4d2})$ or N; and Y^5 is $C(R^{5d2})$ or N; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5d2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1d2} combines with R^{2d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2d2} combines with R^{3d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{4d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3d2} combines with R^{4d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{5d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4d2} combines with R^{5d2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1d2}, R^{2d2}, and R^{3d2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$, then:

Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; or

Y^1 is $C(R^{1e2'})$ or N; Y^2 is $C(R^{2e2'})$ or N; Y^3 is $C(R^{3e2'})$ or N; Y^4 is $C(R^{4e2'})$ or N; and Y^5 is $C(R^{5e2'})$ or N, wherein at least one of Y^1, Y^2, Y^3, Y^4, and Y^5 is N; wherein

R^{1e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5e2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1e2} is Cl; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl, NO_2, or SO_2-C_{1-6} alkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} is NO_2; R^{2e2} is H; R^{3e2} is C_{1-6} haloalkyl; R^{4e2} is H; and R^{5e2} is H; or

R^{1e2} combines with R^{2e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring and R^{3e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2e2} combines with R^{3e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{4e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3e2} combines with R^{4e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{5e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4e2} combines with R^{5e2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1e2}, R^{2e2}, and R^{3e2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{1e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{2e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{3e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{4e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl;

$R^{5e2'}$ is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

$R^{1e2'}$ combines with $R^{2e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{3e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{2e2'}$ combines with $R^{3e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{4e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{3e2'}$ combines with $R^{4e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{5e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

$R^{4e2'}$ combines with $R^{5e2'}$ to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and $R^{1e2'}$, $R^{2e2'}$, and $R^{3e2'}$ are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1f}R^{1f'}$, X^2 is $CR^{2f}R^{2f'}$, and X^3 is a bond; then Y^1 is $C(R^{1f2})$ or N; Y^2 is $C(R^{2f2})$ or N; Y^3 is $C(R^{3f2})$ or N; Y^4 is $C(R^{4f2})$ or N; and Y^5 is $C(R^{5f2})$ or N; wherein

R^{1f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5f2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1f2} combines with R^{2f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2f2} combines with R^{3f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{4f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3f2} combines with R^{4f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{5f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4f2} combines with R^{5f2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1f2}, R^{2f2}, and R^{3f2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1g} or O, X^2 is $CR^{2g}R^{2g'}$, and X^3 is a bond; then Y^1 is $C(R^{1g2})$ or N; Y^2 is $C(R^{2g2})$ or N; Y^3 is $C(R^{3g2})$ or N; Y^4 is $C(R^{4g2})$ or N; and Y^5 is $C(R^{5g2})$ or N; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5g2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1g2} combines with R^{2g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2g2} combines with R^{3g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{4g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3g2} combines with R^{4g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{5g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4g2} combines with R^{5g2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1g2}, R^{2g2}, and R^{3g2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is $CR^{1h}R^{1h'}$, X^2 is NR^{2h} or O, and X^3 is a bond; then Y^1 is $C(R^{1h2})$ or N; Y^2 is $C(R^{2h2})$ or N; Y^3 is $C(R^{3h2})$ or N; Y^4 is $C(R^{4h2})$ or N; and Y^5 is $C(R^{5h2})$ or N; wherein

R^{1h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5h2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1h2} combines with R^{2h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2h2} combines with R^{3h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{4h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3h2} combines with R^{4h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{5h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4h2} combines with R^{5h2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1h2}, R^{2h2}, and R^{3h2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1i} or O, X^2 is C(O), and X^3 is $CR^{3i}R^{3i'}$; then Y^1 is $C(R^{1i2})$ or N; Y^2 is $C(R^{2i2})$ or N; Y^3 is $C(R^{3i2})$ or N; Y^4 is $C(R^{4i2})$ or N; and Y^5 is $C(R^{5i2})$ or N; wherein

R^{1i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5i2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1i2} combines with R^{2i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2i2} combines with R^{3i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{4i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3i2} combines with R^{4i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{5i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4i2} combines with R^{5i2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1i2}, R^{2i2}, and R^{3i2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1j} or O, X^2 is NR^{2j} or O, and X^3 is $CR^{3j}R^{3j'}$; then Y^1 is $C(R^{1j2})$ or N; Y^2 is $C(R^{2j2})$ or N; Y^3 is $C(R^{3j2})$ or N; Y^4 is $C(R^{4j2})$ or N; and Y^5 is $C(R^{5j2})$ or N; wherein

R^{1j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5j2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1j2} combines with R^{2j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{3j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2j2} combines with R^{3j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{4j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3j2} combines with R^{4j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{5j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4j2} combines with R^{5j2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1j2}, R^{2j2}, and R^{3j2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{1k} or O, X^2 is NR^{2k} or O, and X^3 is a bond; then Y^1 is $C(R^{1k2})$ or N; Y^2 is $C(R^{2k2})$ or N; Y^3 is $C(R^{3k2})$ or N; Y^4 is $C(R^{4k2})$ or N; and Y^5 is $C(R^{5k2})$ or N; wherein

R^{1k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5k2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1k2} combines with R^{2k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2k2} combines with R^{3k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{4k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3k2} combines with R^{4k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{5k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4k2} combines with R^{5k2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1k2}, R^{2k2}, and R^{3k2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

if X^1 is NR^{11} or O, X^2 is C(O), and X^3 is NR^{31} or O; then Y^1 is $C(R^{112})$ or N; Y^2 is $C(R^{212})$ or N; Y^3 is $C(R^{312})$ or N; Y^4 is $C(R^{412})$ or N; and Y^5 is $C(R^{512})$ or N; wherein

R^{112} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{212} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{312} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{412} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{512} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{112} combines with R^{212} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{312}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{212} combines with R^{312} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{412}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{312} combines with R^{412} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{112}, R^{212}, and R^{512} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{412} combines with R^{512} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be

unsubstituted or substituted with C_{1-6} alkyl, and R^{1l2}, R^{2l2}, and R^{3l2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN;

or

if X^1 is $CR^{1m}R^{1m'}$, X^2 is $CR^{2m}R^{2m'}$, and X^3 is $CR^{3m}R^{3m'}$-$CR^{4m}R^{4m'}$; then Y^1 is $C(R^{1m2})$ or N; Y^2 is $C(R^{2m2})$ or N; Y^3 is $C(R^{3m2})$ or N; Y^4 is $C(R^{4m2})$ or N; and Y^5 is $C(R^{5m2})$ or N; wherein

R^{1m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{2m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{3m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{4m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl;

R^{5m2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, or SO_2-C_{1-6} alkyl; or

R^{1m2} combines with R^{2m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{3m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{2m2} combines with R^{3m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{4m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{3m2} combines with R^{4m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{5m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN; or

R^{4m2} combines with R^{5m2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with C_{1-6} alkyl, and R^{1m2}, R^{2m2}, and R^{3m2} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, and CN.

93. The method of claim 92, wherein:

X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$;

X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$;

X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O;

X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$;

X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$;

X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; or

X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l};

Z^1 and Z^2 are each independently selected from C(O) and $S(O_2)$;

R^{1a} and $R^{1a'}$ are each independently selected from H, C_{1-6} alkyl, and -CO(O)-C_{1-6} alkyl;

R^{2a} and $R^{2a'}$ are each independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

R^{3a} and $R^{3a'}$ are each independently selected from H and C_{1-6} alkyl;

If Z^1 and Z^2 are both C(O), then at least one of R^{1a}, $R^{1a'}$, R^{2a}, $R^{2a'}$, R^{3a}, or $R^{3a'}$ is C_{1-6} alkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the aryl of R^{2a} or $R^{2a'}$ is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^{1a} and $R^{1a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{2a}, $R^{2a'}$, R^{3a}, and $R^{3a'}$ are each H; orR^{2a} and $R^{2a'}$ combine to form a cycloalkyl ring or heterocyclic ring, and R^{1a}, $R^{1a'}$, R^{3a}, and $R^{3a'}$ are each H; or

R^{1a} and R^{3a} combine to form a cycloalkyl ring, wherein the cycloalkyl ring may be unsubstituted or substituted with one or more C_{1-6} alkyl, and $R^{1a'}$, R^{2a}, $R^{2a'}$, and $R^{3a'}$ are each independently selected from the group consisting of H and C_{1-6} alkyl;R^{1b} is C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{1b} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{3b} and $R^{3b'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1c}, $R^{1c'}$, R^{2c}, and $R^{2c'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1d}, $R^{1d'}$, R^{3d}, and $R^{3d'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1e}, $R^{1e'}$, R^{3e}, and $R^{3e'}$ are each independently selected from H and C_{1-6} alkyl;

R^{1g} is aryl;

wherein the aryl of R^{1g} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{1l} and R^{3l} are each independently selected from H, C_{1-6} alkyl, and aryl;

wherein the aryl of R^{1l} or R^{3l} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

wherein:

if X^1 is $CR^{1a}R^{1a'}$, X^2 is $CR^{2a}R^{2a'}$, and X^3 is $CR^{3a}R^{3a'}$, then:

Y^1 is C(H); Y^2 is C(H) or N; Y^3 is $C(CF_3)$; Y^4 is C(H) or N; and Y^5 is C(H); or

Y^1 is $C(R^{1a2})$; Y^2 is $C(R^{2a2})$; Y^3 is $C(R^{3a2})$; Y^4 is $C(R^{4a2})$; and Y^5 is $C(R^{5a2})$; wherein

R^{1a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5a2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is NR^{1b}, X^2 is CH_2, and X^3 is $CR^{3b}R^{3b'}$; then Y^1 is $C(R^{1b2})$; Y^2 is $C(R^{2b2})$; Y^3 is $C(R^{3b2})$; Y^4 is $C(R^{4b2})$; and Y^5 is $C(R^{5b2})$; wherein

R^{1b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{2b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{3b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{4b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

R^{5b2} is H, halo, C_{1-6} haloalkyl, SO_2-C_{1-6} alkyl, or NO_2;

if X^1 is $CR^{1c}R^{1c'}$, X^2 is $CR^{2c}R^{2c'}$, and X^3 is O; then Y^1 is $C(R^{1c2})$; Y^2 is $C(R^{2c2})$; Y^3 is $C(R^{3c2})$; Y^4 is $C(R^{4c2})$; and Y^5 is $C(R^{5c2})$; wherein

R^{1c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5c2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1d}R^{1d'}$, X^2 is O, S, or $S(O_2)$, and X^3 is $CR^{3d}R^{3d'}$, then Y^1 is $C(R^{1d2})$; Y^2 is $C(R^{2d2})$; Y^3 is $C(R^{3d2})$; Y^4 is $C(R^{4d2})$; and Y^5 is $C(R^{5d2})$; wherein

R^{1d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5d2} is H, halo, C_{1-6} haloalkyl, or NO_2;

if X^1 is $CR^{1e}R^{1e'}$, X^2 is C(O), and X^3 is $CR^{3e}R^{3e'}$; then Y^1 is $C(R^{1e2})$; Y^2 is $C(R^{2e2})$; Y^3 is $C(R^{3e2})$; Y^4 is $C(R^{4e2})$; and Y^5 is $C(R^{5e2})$; wherein

R^{1e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{2e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{3e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{4e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2;

R^{5e2} is H, halo, C_{1-6} haloalkyl, CN, SO_2-C_{1-6} alkyl, or NO_2; or

R^{1e2} combines with R^{2e2} to form a heteroaryl ring, and R^{3e2}, R^{4e2}, and R^{5e2} are each H;

if X^1 is NR^{1g}, X^2 is CH_2, and X^3 is a bond; then Y^1 is $C(R^{1g2})$; Y^2 is $C(R^{2g2})$; Y^3 is $C(R^{3g2})$; Y^4 is $C(R^{4g2})$; and Y^5 is $C(R^{5g2})$; wherein

R^{1g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{2g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{3g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{4g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

R^{5g2} is H, halo, C_{1-6} haloalkyl, or NO_2;

or

if X^1 is NR^{1l}, X^2 is C(O), and X^3 is NR^{3l}; then Y^1 is $C(R^{1l2})$; Y^2 is $C(R^{2l2})$; Y^3 is $C(R^{3l2})$; Y^4 is $C(R^{4l2})$; and Y^5 is $C(R^{5l2})$; wherein

R^{1l2} is H, C_{1-6} haloalkyl, or NO_2;

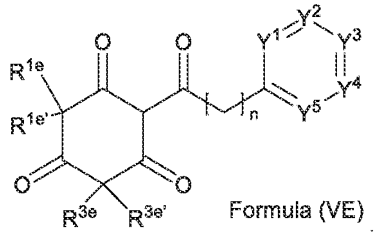
R^{2l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{3l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{4l2} is H, C_{1-6} haloalkyl, or NO_2;

R^{5l2} is H, C_{1-6} haloalkyl, or NO_2.

94. The method of claim 92 or 93, wherein the compound is of Formula (VE), or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof:



Formula (VE)

95. The method of any one of claims 92-94, wherein n is 0.

96. The method of any one of claims 92-95, wherein Y^1 is $C(NO_2)$.

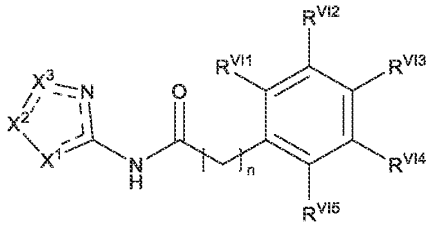
97. The method of any one of claims 92-96, wherein Y^3 is $C(CF_3)$.

98. The method of any one of claims 92-97, wherein R^{1a} and $R^{1a'}$, R^{1c} and $R^{1c'}$, R^{1d} and $R^{1d'}$, R^{1e} and $R^{1e'}$, R^{1f} and $R^{1f'}$, or R^{1h} and $R^{1h'}$ are each CH_3.

99. The method of any one of claims 92-98, wherein R^{3a} and $R^{3a'}$, R^{3b} and $R^{3b'}$, R^{3d} and $R^{3d'}$, R^{3e} and $R^{3e'}$, R^{3i} and $R^{3i'}$, or R^{3j} and $R^{3j'}$ are each CH_3.

100. The method of any one of claims 92-97 or 99, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{1b} is cycloalkyl or heteroaryl.

101. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VI):



Formula (VI)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ═══ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

X^1 is NR^1, X^2 is CR^2, and X^3 is N or CH;

X^1 is O, X^2 is CR^2, and X^3 is N;

X^1 is N, X^2 is NR^1, and X^3 is N; or

X^1 is NR^3, X^2 is N, and X^3 is N;

n is 0 or 1;

R^1 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^1 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^2 is selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, SO_2-C_{1-6} alkyl, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, and heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

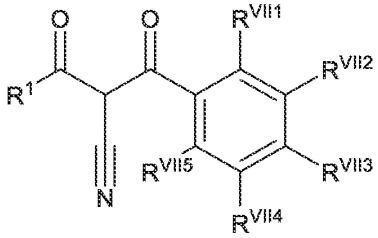
R^{VI1}, R^{VI2}, R^{VI3}, R^{VI4}, and R^{VI5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

102. The method of claim 101, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^3 is C_{4-6} alkyl or phenyl substituted with one or more halo.

103. The method of claim 101 or 102, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{VII1} is NO_2.

104. The method of any one of claims 101-103, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{VII3} is CF_3.

105. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VII):



Formula (VII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

R^1 is selected from the group consisting of C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, and C_1 alkyl-heteroaryl;

wherein the C_{3-6} cycloalkyl, C_1 alkyl-C_{3-6} cycloalkyl, aryl, C_1 alkyl-aryl, heteroaryl, or C_1 alkyl-heteroaryl of R^1 is unsubstituted or substituted with halo;

R^{VII1}, R^{VII2}, R^{VII3}, R^{VII4}, and R^{VII5} are each independently selected from H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl.

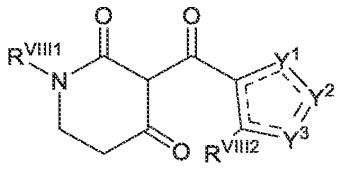
106. The method of claim 105, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1 is aryl or C_1 alkyl-aryl, wherein the aryl or C_1 alkyl-aryl may be unsubstituted or substituted with one or more halo.

107. The method of claim 105 or 106, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{VIII1} is H or NO_2.

108. The method of any one of claims 105-107, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{VII2} is H, halo, or SO_2-C_{1-6} alkyl.

109. The method of any one of claims 105-108, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^{VII3} is CF_3.

110. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula (VIII):



Formula (VIII)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein each ≡≡≡ independently represents a single bond or a double bond, subject to the satisfaction of valency requirements, wherein:

Y^1 is CR^1, Y^2 is N, and Y^3 is NR^3;

Y^1 is CR^1, Y^2 is O or S, and Y^3 is CR^3;

Y^1 is N, Y^2 is CR^2, and Y^3 is O or S; or

Y^1 is O or S, Y^2 is CR^2, and Y^3 is CR^3;

R^1 and R^2 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, and aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^1 or R^2 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^3 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl;

wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, -CO(O)-C_{1-6} alkyl, or aryl of R^3 is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl; or

R^3 combines with R^{VIII2} to form an aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring, wherein the aryl ring, heteroaryl ring, cycloalkyl ring, or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl;

R^{VIII1} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl;

wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, C_{1-6} alkyl-aryl, or heteroaryl of R^{VIII1} is unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, and alkoxy;

R^{VIII2} is H, halo, C_{1-6} haloalkyl, NO_2, CN, and SO_2-C_{1-6} alkyl; or

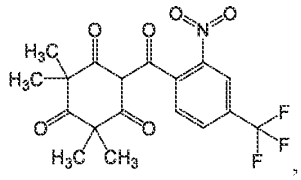
R^{VIII2} combines with R^3 to form a cycloalkyl ring or heterocyclic ring, wherein the cycloalkyl ring or heterocyclic ring may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, alkoxy, C_{1-6} alkyl, C_{1-6} haloalkyl, and -CO(O)-C_{1-6} alkyl.

111. The method of claim 110, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1 is CF_3.

112. The method of claim 110 or 111, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^2 is CF_3.

113. The method of any one of claims 110-112, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^3 is C_{1-6} alkyl.

114. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound, wherein the compound is



, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

115. A method of treating a condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

116. Use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering to the subject an effective amount of the compound of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG-N), Formula (IG-N3), Formula (IG-O), Formula (IH-N), Formula (IH-N3), Formula (IH-O), Formula (Ii-N), Formula (Ii-N3), Formula (IJ-N), Formula (IJ-N3), Formula (IK-N), Formula (IK-N3), Formula (IL-N), Formula (IL-N3), Formula (IM), Formula (II), Formula (IIA-C), Formula (IIA-C3), Formula (IIA-N), Formula (IIA-N3), Formula (IIB), Formula (IIB3), Formula (IIC), Formula (IIC3), Formula (IID), Formula (III), Formula (IV), Formula (IVA), Formula (IVA3), Formula (IVB-O), Formula (IVB-O3), Formula (IVB-S), Formula (IVB-S3), Formula (IVC-S), Formula (IVC-S3), Formula (IVD), Formula (IVD3), Formula (V), Formula (VE), Formula (VI), Formula (VII), Formula (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

117. Use of the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering to the subject an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

118. Use of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof,

wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG-N), Formula (IG-N3), Formula (IG-O), Formula (IH-N), Formula (IH-N3), Formula (IH-O), Formula (Ii-N), Formula (Ii-N3), Formula (IJ-N), Formula (IJ-N3), Formula (IK-N), Formula (IK-N3), Formula (IL-N), Formula (IL-N3), Formula (IM), Formula (II), Formula (IIA-C), Formula (IIA-C3), Formula (IIA-N), Formula (IIA-N3), Formula (IIB), Formula (IIB3), Formula (IIC), Formula (IIC3), Formula (IID), Formula (III), Formula (IV), Formula (IVA), Formula (IVA3), Formula (IVB-O), Formula (IVB-O3), Formula (IVB-S), Formula (IVB-S3), Formula (IVC-S), Formula (IVC-S3), Formula (IVD), Formula (IVD3), Formula (V), Formula (VE), Formula (VI), Formula (VII), Formula (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

119. Use of the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment of a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof,

wherein the medicament comprises an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.

120. A compound for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject,

wherein the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG-N), Formula (IG-N3), Formula (IG-O), Formula (IH-N), Formula (IH-N3), Formula (IH-O), Formula (Ii-N), Formula (Ii-N3), Formula (IJ-N), Formula (IJ-N3), Formula (IK-N), Formula (IK-N3), Formula (IL-N), Formula (IL-N3), Formula (IM), Formula (II), Formula (IIA-C), Formula (IIA-C3), Formula (IIA-N), Formula (IIA-N3), Formula (IIB), Formula (IIB3), Formula (IIC), Formula (IIC3), Formula (IID), Formula (III), Formula (IV), Formula (IVA), Formula (IVA3), Formula (IVB-O), Formula (IVB-O3), Formula (IVB-S), Formula (IVB-S3), Formula (IVC-S), Formula (IVC-S3), Formula (IVD), Formula (IVD3), Formula (V), Formula (VE), Formula (VI), Formula (VII), Formula (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

121. The compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, for use in a method of treating a condition that is responsive to modulation or inhibition of HPD in a human subject in need thereof, the method comprising:

administering an effective amount of the compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, to the subject.

122. A pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein:

the method comprises administering the pharmaceutical formulation to a subject having the condition; and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG-N), Formula (IG-N3), Formula (IG-O), Formula (IH-N), Formula (IH-N3), Formula (IH-O), Formula (Ii-N), Formula (Ii-N3), Formula (IJ-N), Formula (IJ-N3), Formula (IK-N), Formula (IK-N3), Formula (IL-N), Formula (IL-N3), Formula (IM), Formula (II), Formula (IIA-C), Formula (IIA-C3), Formula (IIA-N), Formula (IIA-N3), Formula (IIB), Formula (IIB3), Formula (IIC), Formula (IIC3), Formula (IID), Formula (III), Formula (IV), Formula (IVA), Formula (IVA3), Formula (IVB-O), Formula (IVB-O3), Formula (IVB-S), Formula (IVB-S3), Formula (IVC-S), Formula (IVC-S3), Formula (IVD), Formula (IVD3), Formula (V), Formula (VE), Formula (VI), Formula (VII), Formula (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

123. A pharmaceutical formulation for use in a method of treating a condition that is responsive to modulation or inhibition of HPD, the formulation comprising an effective amount of the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, wherein:

the method comprises administering the pharmaceutical formulation to a subject having the condition.

124. A medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of a compound, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

the treatment comprises administering the medicament to a subject having the condition; and

the compound is of Formula (I), Formula (IA), Formula (IA3), Formula (IB-N), Formula (IB-N3), Formula (IB-O), Formula (IC-N), Formula (IC-N3), Formula (IC-O), Formula (ID-O), Formula (ID-S), Formula (ID-SO2), Formula (IE), Formula (IF), Formula (IG-N), Formula (IG-N3), Formula (IG-O), Formula (IH-N), Formula (IH-N3), Formula (IH-O), Formula (Ii-N), Formula (Ii-N3), Formula (IJ-N), Formula (IJ-N3), Formula (IK-N), Formula (IK-N3), Formula (IL-N), Formula (IL-N3), Formula (IM), Formula (II), Formula (IIA-C), Formula (IIA-C3), Formula (IIA-N), Formula (IIA-N3), Formula (IIB), Formula (IIB3), Formula (IIC), Formula (IIC3), Formula (IID),

Formula (III), Formula (IV), Formula (IVA), Formula (IVA3), Formula (IVB-O), Formula (IVB-O3), Formula (IVB-S), Formula (IVB-S3), Formula (IVC-S), Formula (IVC-S3), Formula (IVD), Formula (IVD3), Formula (V), Formula (VE), Formula (VI), Formula (VII), Formula (VIII), or a pharmaceutically acceptable salt, stereoisomer, or tautomer of any of the foregoing.

125. A medicament for treating a condition that is responsive to modulation or inhibition of HPD, the medicament comprising an effective amount of the compound of any one of claims 1-90, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein:

the treatment comprises administering the medicament to a subject having the condition.

126. The method of any one of claims 92-115, wherein the condition is responsive to modulation or inhibition of HPD.

127. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-126, wherein the condition is an inborn error of metabolism.

128. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 127, wherein the inborn error of metabolism is an inborn error of tyrosine metabolism.

129. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 128, wherein the inborn error of tyrosine metabolism is tyrosinemia type I, tyrosinemia type II, tyrosinemia type III, alkaptonuria, or hawkinsinuria.

130. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 127, wherein the inborn error of metabolism is an inborn error of phenylalanine metabolism.

131. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 130, wherein the inborn error of phenylalanine metabolism is phenylketonuria.

132. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-126, wherein the condition is selected from the group consisting of myalgic encephalomyelitis, Parkinson's disease, Lewy Body dementia, mood disorders, autoimmune disorders, inflammatory disorders, neuropathic pain, refractory hypertension, low sex drive, attention-deficit/hyperactivity disorder (ADHD), sleep disorders, restless leg syndrome, obsessive-compulsive disorder (OCD), panic disorders, post-traumatic stress disorder (PTSD), substance abuse disorders, chronic constipation, tremor disorders, CoQ10 deficiency, and oculocutaneous albinism.

133. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-132, further comprising administering low-protein diet to the subject, wherein the low-protein diet comprises less than about 2 g/day of protein.

134. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-133, further comprising administering a dietary product to the subject.

135. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 134, wherein the dietary product comprises less than 25% of a recommended dietary allowance (RDA) of tyrosine for the subject's age group, less than 25% of an RDA of phenylalanine for the subject's age group, or less than 25% of an RDA of tyrosine and phenylalanine for the subject's age group.

136. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 135, wherein the RDA for the subject's age group is as determined by the Food and Nutrition Board of the Institute of Medicine.

137. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-136, wherein the dietary product comprises less than 25% of an average recommended dietary intake of tyrosine for the subject's age group, less than 25% of an average

recommended dietary intake of phenylalanine for the subject's age group, or less than 25% of an average recommended dietary intake of tyrosine and phenylalanine for the subject's age group.

138. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 137, wherein the average recommended dietary intake is an RDA for the subject's age group is determined by the Food and Nutrition Board of the Institute of Medicine.

139. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-138, wherein the dietary product comprises less than a daily recommended amount of phenylalanine and tyrosine combined.

140. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 139, wherein the daily recommended amount of phenylalanine and tyrosine is 33 mg/kg/day.

141. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-140, wherein the dietary product comprises less than 25% of a median dietary intake of tyrosine in a control or healthy subject of the same age group as the subject, less than 25% of a median dietary intake of phenylalanine in a control or healthy subject of the same age group as the subject or less than 25% of a median dietary intake of tyrosine and phenylalanine in a control or healthy subject of the same age group as the subject.

142. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 134, wherein the dietary product is devoid of tyrosine, devoid of phenylalanine, or devoid of tyrosine and devoid of phenylalanine.

143. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-142, wherein the dietary product is administered orally.

144. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claims 134-143, wherein the dietary product is formulated as a solid or as a beverage.

145. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claims 134-144, wherein the dietary product is administered via tube.

146. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 145, wherein the dietary product is administered via nasogastric tube.

147. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-146, wherein the dietary product is administered intravenously or parenterally.

148. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-147, wherein the subject is administered a therapeutically effective amount of the dietary product.

149. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 148, wherein the therapeutically effective amount of the dietary product is from about 0.5 g/kg/day to about 1 g/kg/day.

150. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 148 or 149, wherein the therapeutically effective amount of the dietary product is about 0.8 g/kg/day.

151. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-150, wherein the dietary product is administered with food.

152. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-151, wherein the dietary product is administered 3 times a day or 5 times a day.

153. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-152, wherein the dietary product is a sole source of amino acids for the subject.

154. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 134-153, wherein the dietary product is a sole source of calories for the subject.

155. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-154, wherein the administering is oral or via tube.

156. The method, the use, the compound, the pharmaceutical formulation, or the medicament of claim 155, wherein the administering is via nasogastric tube.

157. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-154, wherein the administering is intravenous.

158. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-157, wherein the administering is once daily or twice daily.

159. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-158, wherein the administering is with food.

160. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-158, wherein the subject is in a fasted state.

161. The method, the use, the compound, the pharmaceutical formulation, or the medicament of any one of claims 92-160, wherein the compound is administered in a pharmaceutical composition, wherein the pharmaceutical composition is in unit dosage form, the unit dosage form comprising a pharmaceutically acceptable excipient.

162. An herbicidal composition comprising the compound of any one of claims 1-90, or an agriculturally acceptable salt thereof.

163. The herbicidal composition of claim 162, further comprising an herbicidal safener, wherein the herbicidal safener increases a metabolic rate of the herbicidal composition in a crop.

164. The herbicidal composition of claim 163, wherein the herbicidal safener increases expression of a gene that encodes an enzyme responsible for xenobiotic degradation of the herbicidal composition in the crop.

165. The herbicidal composition of claim 164, wherein the gene encodes Cytochrome P450, glutathione-S-transferase, or an ATP-binding cassette transporter.

166. The herbicidal composition of any one of claims 163-165, wherein the herbicidal safener is identified in a biological screen.

167. The herbicidal composition of any one of claims 163-166, wherein the herbicidal composition and the herbicidal safener are present in a ratio of at least 4:1 by weight (compound:safener).

168. The herbicidal composition of any one of claims 163-167, wherein the herbicidal safener comprises fluroxypyr-meptyl.

169. The herbicidal composition of any one of claims 162-168, further comprising a second herbicide.

170. The herbicidal composition of claim 169, wherein the second herbicide does not inhibit HPD.

171. The herbicidal composition of claim 169 or 170, wherein the second herbicide shows synergistic effects with the herbicidal composition.

172. The herbicidal composition of any one of claims 169-171, wherein the second herbicide is a photosystem II inhibitor herbicide, an acetolactate synthase inhibitor, 5-enolpyruvlshikimate 3-phosphate synthase inhibitor, a very long-chain fatty acid biosynthesis inhibitor, an acetyl-coenzyme A carboxylase inhibitor, a synthetic auxin, a protoporphyrinogen oxidase inhibitor, a microtubule inhibitor, a carotenoid biosynthesis inhibitor, a glutamine synthetase inhibitor, or a photosystem I electron driver.

173. A method of controlling a weed, comprising contacting the weed with the herbicidal composition of any one of claims 162-172.

174. The method of claim 173, comprising contacting the weed with an effective amount of the herbicidal composition.

175. The method of claim 173 or 174, wherein the weed is selected from the group consisting of a dicotyledonous weed and a monocotyledonous weed.

176. The method of any one of claims 173-175, wherein the weed has an acquired resistance to an herbicide.

177. The method of claim 176, wherein the weed is an acetyl-coenzyme A carboxylase-resistant weed, an acetolactate synthase-resistant weed, a glyphosate-resistant weed, a paraquat-resistant weed, an aminopyralid + 2,4-D-resistant weed, a picloram-resistant weed, a 2,4-dichlorophenoxyacetic acid-resistant weed, a propanil-resistant weed, a 3,4-dichloroaniline + propionic acid-resistant weed, a dichloroaniline-resistant weed, a pendimethalin-resistant weed, or a weed with a combination of any of the foregoing resistances.