(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 June 2016 (30.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/103037 A1

(51) International Patent Classification:
C07D 487/14 (2006.01) *A61P 3/00* (2006.01)
A61K 31/407 (2006.01)

(21) International Application Number:
PCT/IB2015/002549

(22) International Filing Date:
21 December 2015 (21.12.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/095,646 22 December 2014 (22.12.2014) US

(71) Applicant: **AKARNA THERAPEUTICS, LTD.** [GB/GB]; 20-22 Bedford Row, London WC1R 4JS (GB).

(72) Inventors: **MOHAN, Raju**; 3125 Caminito Ricardo, Encinitas, CA 92024 (US). **PRATT, Benjamin, Anthony**; 1057 Guadalajara Drive, Encinitas, CA 92024 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2016/103037 A1

(54) Title: FUSED BICYCLIC COMPOUNDS FOR THE TREATMENT OF DISEASE

(57) Abstract: Described herein are fused bicyclic compounds, compositions, and methods for their use for the treatment of disease.

FUSED BICYCLIC COMPOUNDS FOR THE TREATMENT OF DISEASE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. provisional application Ser. No. 62/095,646, filed December 22, 2014, which is incorporated by reference in its entirety.

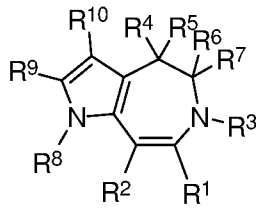
BACKGROUND OF THE INVENTION

[0002] Farnesoid X receptor (FXR) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Bile acids are FXR physiological ligands. On activation by bile acids, FXR regulates a wide variety of target genes that are critically involved in the control of bile acid, lipid and glucose homeostasis. Thus, FXR plays a key role in the pathogenesis of cholestatic diseases, non-alcoholic fatty liver disease and inflammatory bowel disease.

SUMMARY OF THE INVENTION

[0003] Described herein are compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), pharmaceutical compositions that include such compounds, and methods of use thereof, for modulating FXR. In one aspect is the administration of at least one FXR modulator described herein to a mammal in the treatment of diseases, disorders or conditions that would benefit from FXR modulation.

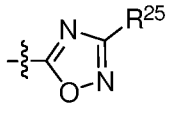
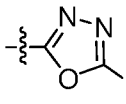
[0004] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, $-C(O)N(R^{25})R^{26}$,  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^3 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, optionally substituted -(C_1-C_2alkylene)-(heteroaryl), $-C(O)R^{20}$, $-C(O)OR^{20}$, $-S(O)_2R^{20}$, $-C(O)N(R^{21})R^{22}$, $-C(O)N(R^{21})S(O)_2R^{24}$, $-C(O)N(R^{23})N(R^{21})R^{22}$, $-C(O)N(R^{23})N(R^{21})S(O)_2R^{24}$, $-N(R^{23})C(O)R^{20}$, $-N(R^{23})C(O)N(R^{21})R^{22}$, $-N(R^{23})C(O)N(R^{21})S(O)_2R^{24}$, $-N(R^{20})C(O)N(R^{23})N(R^{21})R^{22}$, $-N(R^{20})C(O)N(R^{23})N(R^{21})S(O)_2R^{24}$, $-N(R^{23})C(O)OR^{20}$, $-P(O)OR^{20}$, and $-P(O)(OR^{19})OR^{20}$;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and $-C(O)N(R^{27})R^{28}$;

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{19}, R^{20}, and R^{23} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted

C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

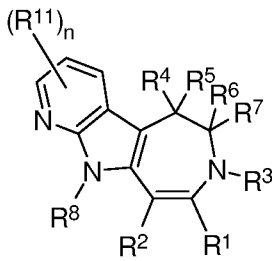
R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{21} and R^{22} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{24} is selected from the group consisting of optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted, aryl optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); and

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring.

[0005] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ia);

wherein:

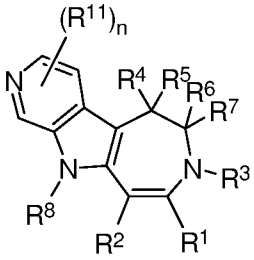
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0006] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ib);

wherein:

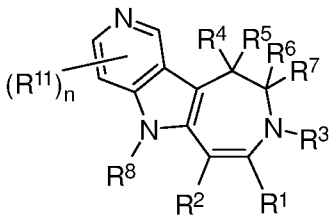
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0007] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ic), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ic);

wherein:

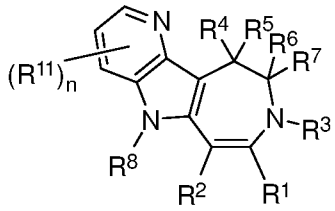
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0008] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Id), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Id);

wherein:

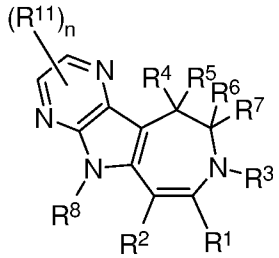
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0009] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ie), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ie);

wherein:

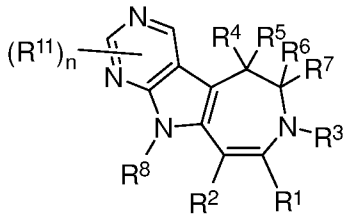
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0010] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (If), or a pharmaceutically acceptable salt or solvate thereof:



Formula (If);

wherein:

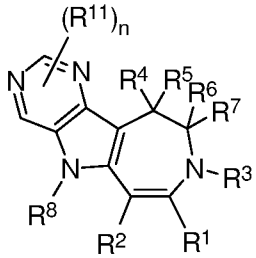
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0011] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ig), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ig);

wherein:

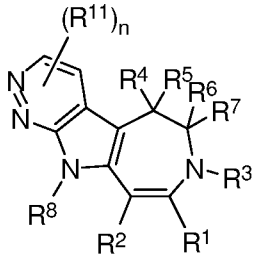
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0012] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ih), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ih);

wherein:

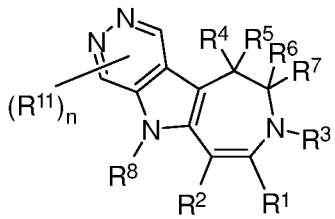
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0013] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ii), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ii);

wherein:

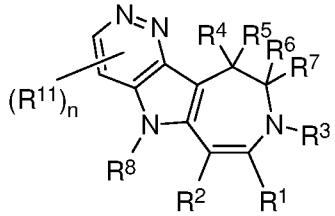
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0014] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ij), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ij);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

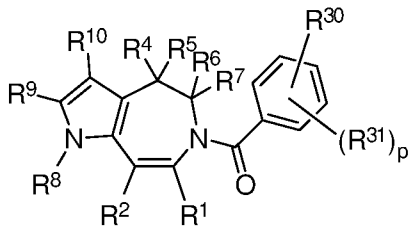
each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0015] In one embodiment is a compound of Formula (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^6 and R^7 are hydrogen. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are C_1-C_6alkyl. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are methyl. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate,

or prodrug thereof, wherein R^3 is $-C(O)N(R^{21})R^{22}$. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is $-C(O)N(R^{21})R^{22}$ and R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is $-C(O)R^{20}$. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is $-C(O)R^{20}$ and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is $-S(O)_2R^{20}$. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), or (Ij), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is $-S(O)_2R^{20}$ and R^{20} is optionally substituted aryl.

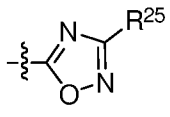
[0016] In another aspect provided herein is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:

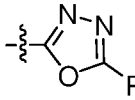


Formula (II);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, $-C(O)N(R^{25})R^{26}$, 

, and 

; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -$C(O)N(R^{27})R^{28}$;

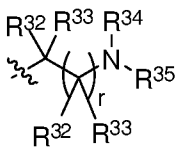
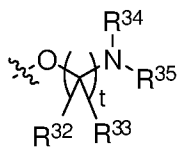
R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen,  , or  ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

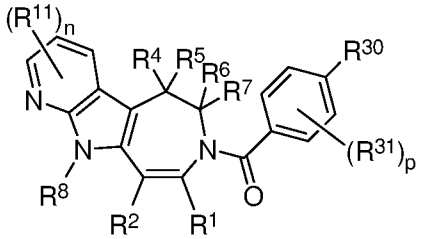
R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

[0017] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa);

wherein:

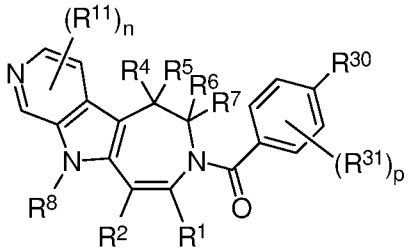
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0018] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIb);

wherein:

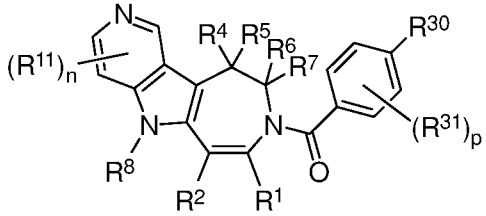
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0019] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIc), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIc);

wherein:

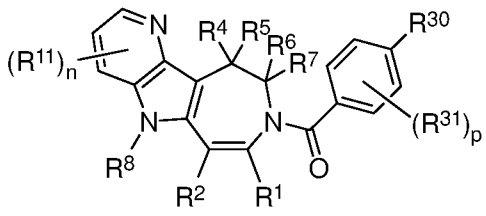
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0020] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IId), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IId);

wherein:

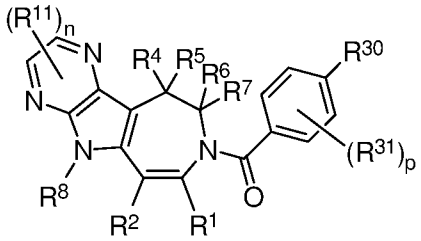
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0021] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIe), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIe);

wherein:

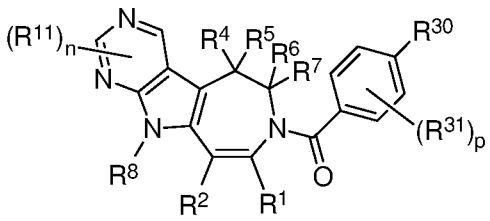
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0022] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIf), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIf);

wherein:

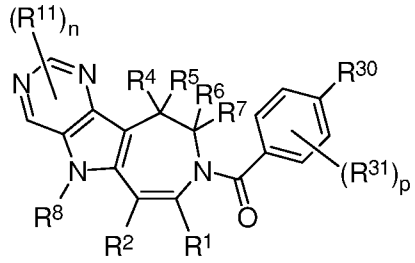
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0023] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIg), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIg);

wherein:

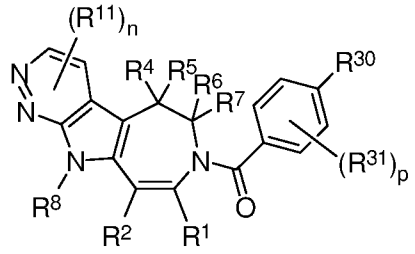
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0024] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIh), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIh);

wherein:

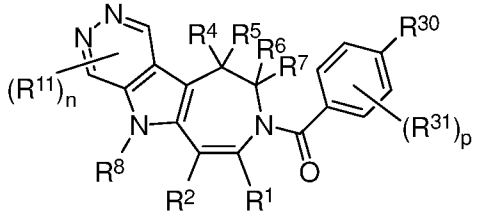
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0025] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIi), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIi);

wherein:

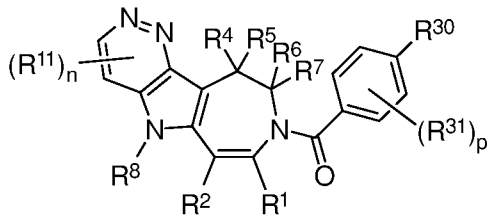
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0026] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIj), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIj);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

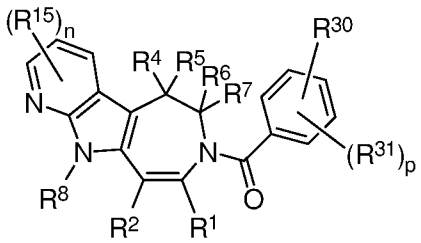
each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[0027] In one embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0. In another embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), or (IIj), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 2 and each R^{11} is independently selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy.

[0028] In another aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:

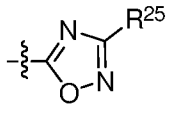
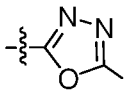


Formula (III);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-

C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

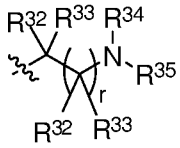
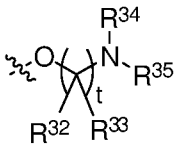
each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14}, -OC(O)OR^{12}, -OC(O)N(R^{13})R^{14}, -N(R^{13})C(O)OR^{12}, and -N(R^{13})C(O)N(R^{13})R^{14};

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl,

optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl,  ,  or ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

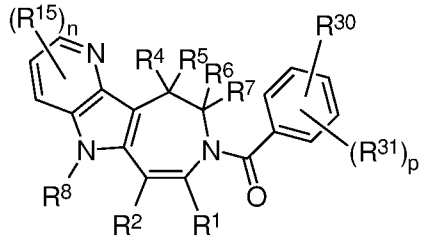
n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

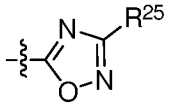
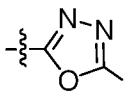
[0029] In another aspect, provided herein is a compound having the structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

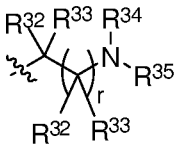
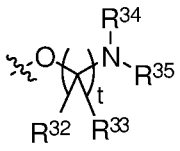
each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14}, -OC(O)OR^{12}, -OC(O)N(R^{13})R^{14}, -N(R^{13})C(O)OR^{12}, and -N(R^{13})C(O)N(R^{13})R^{14};

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl,  ,  or ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-

C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

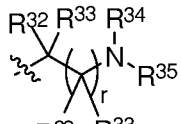
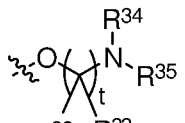
n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

[0030] In one embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0. In another embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is halogen. In another embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is C_1-C_6alkyl. In another embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 2 and each R^{15} is independently selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy.

[0031] In another embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is F. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is  . In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is  . In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein p is 1. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or

prodrug thereof, wherein R^{31} is halogen. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{31} is F. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^6 and R^7 are hydrogen. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are C_1-C_6alkyl. In a further embodiment is a compound of Formula (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are methyl.

[0032] In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)OR^{25}. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)OR^{25} and R^{25} is C_1-C_6alkyl. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)OR^{25} and R^{25} is methyl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)OR^{25} and R^{25} is ethyl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)OR^{25} and R^{25} is isopropyl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)N(R^{25})R^{26} and R^{25} is C_1-C_6alkyl. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is -C(O)N(R^{25})R^{26} and R^{25} is methyl. In another embodiment is a compound of

Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is $-C(O)N(R^{25})R^{26}$ and R^{25} is ethyl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is $-C(O)N(R^{25})R^{26}$ and R^{25} is isopropyl. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is $-C(O)N(R^{25})R^{26}$ and R^{26} is hydrogen. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^1 is hydrogen. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^8 is hydrogen.

[0033] Any combination of the groups described above or below for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0034] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent, excipient or binder. In one embodiment, the pharmaceutical composition comprising the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.

[0035] In another aspect is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering to the mammal a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof.

[0036] In a further embodiment is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering to the mammal a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or

solvate thereof; wherein the disease, disorder or condition in a mammal is nonalcoholic steatohepatitis (NASH), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events, atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis or obesity. In another embodiment is the use of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from FXR modulation. In another embodiment is the use of a FXR modulator in the manufacture of a medicament for use in the treatment of a disease, disorder or condition in a mammal, wherein the disease, disorder or condition in a mammal is nonalcoholic steatohepatitis (NASH), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events, atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis or obesity.

[0037] In another aspect is a method of modulating FXR activity comprising contacting FXR, or portion thereof, with a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof.

INCORPORATION BY REFERENCE

[0038] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0039] The Farnesoid X receptor (FXR; also referred to as NR1H4; nuclear receptor nomenclature committee 1999) is a member of the steroid and thyroid hormone nuclear receptor superfamily of ligand regulated transcription factors. FXR is highly expressed in the liver, kidney, intestines and the adrenals and at lower levels in the vasculature (Forman et al., Cell 1995, 81(5):687-93). Bile acids, the end-products of cholesterol catabolism, bind directly to the ligand binding pocket of FXR and act as agonists to increase the receptor's ability to activate transcription (Makishima et al., Science 1999, 284(5418):1362-5 1999; Mi et al., Mol Cell 2003, 11(4):1093-100; Parks et al., Science 1999, 284(5418):1365-8; Wang et al., Mol Cell 1999, 3(5):543-53). In response to bile acid binding FXR regulates a network of genes that control the

synthesis, transport, and catabolism of bile acids, but also triglycerides and cholesterol (Chawla et al., Cell 2000, 103(1):1-4; Repa and Mangelsdorf, Annu Rev Cell Dev Biol 2000, 16:459-81). Thus FXR functions as a regulator of lipid metabolism by modifying gene expression in response to quantitative changes in the metabolism and breakdown of cholesterol. In support of this conclusion, studies in humans and in animals have demonstrated that modifying bile acid levels can have profound effects on plasma triglyceride and cholesterol levels (Angelin et al., J Lipid Res 1978, 19(8):1017-24; Bateson et al., Br J Clin Pharmacol 1978, 5(3):249-54; Iser and Sali, Drugs 1981, 21(2):90-119; Kuroki et al., Lipids 1999, 34(8):817-23).

[0040] Metabolic disease including obesity, diabetes, hypertension, and cardiovascular disease, are diseases driven by both mulitfactorial genetics (thrifty genotypes) as well as lifestyle habits, and are now reaching epidemic proportions in developed nations. It is believed that increasingly high caloric diets combined with sedentary life styles are major contributors to the growing incidence of these diseases. Importantly hyperlipidemia is associated with many types of metabolic disease, and statistics from the American Heart Association indicate that approximately half of the adult population in the United States has plasma cholesterol levels that put individuals at risk for the development of cardiovascular disease (American Heart Association, Heart disease and stroke statistics – 2005 update; 2005:1-59). Furthermore, the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATPIII, National Cholesterol Education Program 2001) has identified elevated triglyceride levels as an independent risk factor for the development of cardiovascular disease. Approximately one third of the adult population in the United States that have elevated cholesterol levels also have increased triglycerides. The elevation in plasma triglycerides has now been recognized as an early and dominant dyslipidemic symptom in patients with obesity, metabolic syndrome and diabetes and has been suggested to play a causative role in the development of insulin resistance and type II diabetes (Hegarty et al., Acta Physiol Scand 2003;178(4):373-83; Shulman, J Clin Invest 2000;106(2):171-6).

[0041] Current standard of care for hyperlipidemia focuses on lowering low density lipoprotein cholesterol (LDL) using the statin class of hydroxymethyl-glutaryl-CoA reductase inhibitors (National Cholesterol Education Program 2001). However, even after statin therapy a significant number of patients still exhibit elevated levels of plasma triglycerides and triglyceride-rich lipoproteins including very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL) (Friday, Exp Biol Med (Maywood) 2003, 228(7):769-78; Quilliam et al., J Manag Care Pharm 2004, 10(3):244-50). To treat this population of patients with concurrent high plasma triglyceride levels the ATPIII has identified lowering of triglyceride-rich

cholesterol fractions (VLDL + IDL) as a secondary target of drug therapy (National Cholesterol Education Program 2001). Unfortunately treatment of such patients with fibrates, an approved class of triglyceride lowering drugs, has potential adverse side effects, including the possibility of increased LDL cholesterol as well as carrying the risk of fatal rhabdomyolysis, so that combination therapy must proceed cautiously (National Cholesterol Education Program 2001). Similarly nicotinic acid, a second approved triglyceride lowering agent, is contraindicated in patients with insulin resistance and type II diabetes (Capuzzi et al., Curr Atheroscler Rep 2000, 2(1):64-71). Taken together these observations highlight the need for an effective therapeutic agent for the lowering of triglycerides and non-HDL cholesterol in patients with cardiovascular disease, diabetes, and metabolic syndrome.

[0042] The maintenance of lipid homeostasis requires coordinate control of cholesterol and triglyceride synthesis, transport, up-take, and excretion. Interestingly, studies in human and in animal models have uncovered a link between bile acids, the metabolic end-product of cholesterol metabolism, and lipid homeostasis. Clinical studies in the late 1970s exploring the effect of bile acids on cholesterol gallstones demonstrated that treatment with chenodeoxycholic acid (CDCA) reduces plasma triglyceride levels (Bateson et al., Br J Clin Pharmacol 1978, 5(3):249-54; Iser and Sali, Drugs 1981, 21(2):90-119). In contrast, treatment with bile acid sequestrants, which deplete intestinal bile acids, increase triglycerides (Angelin et al., J Lipid Res 1978;19(8):1017-24). Importantly the bile acid-dependent decrease in triglycerides is mediated, at least in part, through a reduction in the production of VLDL (Hirokane et al., J Biol Chem 2004, 279(44):45685-92; Post et al., Arterioscler Thromb Vasc Biol 2004, 24(4):768-74; Sirvent et al., FEBS Lett 2004, 566(1-3):173-7; Kang and Davis, Biochim Biophys Acta 2000, 1529(1-3):223-30). While bile acids are known to mediate the absorption of cholesterol and fat in the intestine the mechanistic basis for the connection between bile acids and lipid levels remained unclear until the recent characterization of FXR.

[0043] The FXR was originally cloned and classified as an orphan member of the nuclear hormone receptor superfamily based upon DNA sequence homology. Initial studies identified farnesol as a ligand for FXR (Forman et al., Cell 1995, 81(5):687-93), however, subsequent analysis demonstrated that bile acids bind directly to the ligand binding domain of FXR and function as activators of the receptor's transcriptional activity. The binding affinities of bile acids for FXR is near the concentration that these compounds reach in animals (μM) lending support to the idea that bile acids function as endogenous ligands in vivo (Makishima et al., Science 1999, 284(5418):1362-5 1999; Mi et al., Mol Cell 2003, 11(4):1093-100; Parks et al., Science 1999, 284(5418):1365-8; Wang et al., Mol Cell 1999, 3(5):543-53). Activation of FXR upon bile acid binding leads to transcriptional down-regulation of cholesterol 7α-hydroxylase

(CYP7A1), the rate limiting enzyme in the conversion of cholesterol to bile acids. Inhibition of CYP7A1 by bile acids occurs via FXR-dependent induction of the small heterodimeric partner (SHP; also referred to as NR0B2, Nuclear Receptor Nomenclature Committee 1999), a transcriptional repressor. Binding sites for FXR have been identified in the SHP promoter indicating that this gene is a direct target of FXR (Lu et al., Mol Cell 2000, 6(3):507-15; Goodwin et al., Mol Cell 2000, 6(3):517-26). Thus bile acid-dependent repression of CYP7A1 is indirect and results from a transcriptional cascade initiated by FXR. A similar SHP-dependent mechanism has been described for the bile acid repression of another gene involved in bile acid synthesis, CYP8B1 (sterol 12α hydroxylase; Yang et al., Biochim Biophys Acta 2002, 1583(1):63-73), and for the sodium/taurocholate cotransporter peptide (NTCP) which is one of two major transporters responsible for bile acid up-take by the liver (Denson et al., Gastroenterology 2001;121(1):140-7). In contrast the genes encoding the bile salt export pump (BSEP) and the multidrug resistance protein 2 (MDR2) are directly induced by FXR, once again via binding sites in their respective promoter regions (Ananthanarayanan et al., J Biol Chem 2001, 276(31):28857-65; Huang et al., J Biol Chem 2003, 278(51):51085-90; Liu et al., J Clin Invest 2003, 112(11):1678-87). These two transporters are required for the transfer of bile acids (BSEP) and phospholipids (MDR2) out of the hepatocytes into the biliary system. This pattern of FXR-dependent gene expression defines a classic feedback loop where high levels of bile acids inhibit new bile acid synthesis and bile acid uptake while simultaneously promoting their own clearance.

[0044] The regulation of bile acid synthesis and transport by FXR has important implications for cholesterol metabolism. Repression of CYP7A1 and CYP8B1 impacts the bile acid synthetic pathway at two important points. First, inhibition of CYP7A1, the rate limiting enzyme, can decrease synthesis and reduce the size of the bile acid pool. Second, inhibition of CYP8B1 alters bile acid composition by favoring the production of more hydrophilic bile acids such as CDCA (muricholic acid/MCA in mice) (Russell, Annu Rev Biochem 2003, 72:137-74). Importantly, studies in mice have demonstrated that the more hydrophilic bile acids are less efficient at promoting intestinal cholesterol absorption (Wang et al., Am J Physiol Gastrointest Liver Physiol 2003, 285(3):G494-502).

[0045] Although regulating bile acid synthesis may contribute to the FXR-dependent effects on lipid metabolism, gene expression analysis indicates that FXR also directly influences triglyceride synthesis and VLDL production. FXR agonists induce the genes encoding fibroblast growth factor 19 (Holt et al., Genes Dev 2003, 17(13):1581-91), acylation stimulating protein (a proteolytic product of complement C3; Li et al., J Biol Chem 2005, 280(9):7427-34), apolipoprotein CII (Kast et al., Mol Endocrinol 2001, 15(10):1720-8), and apolipoprotein AV

(Prieur et al., J Biol Chem 2003, 278(28):25468-80) all of which are known to promote the clearance and oxidation of fat carried by triglyceride rich lipoproteins. Additionally FXR inhibits expression of the genes encoding apolipoprotein CIII (Claudel et al., Gastroenterology 2003, 125(2):544-55), an inhibitor of lipoprotein lipase, and the sterol response element binding protein 1c (SREBP1c; Watanabe et al., J Clin Invest 2004, 113(10):1408-18). SREBP1c, a member of basic helix-loop-helix family of transcription factors, functions as a master transcriptional regulator of the enzymes required for fatty acid synthesis (Osborne, J Biol Chem 2000, 275(42):32379-82). Taken together the genetic network controlled by FXR defines a signal transduction system poised to respond to changes in fat and carbohydrate dietary intake-driven lipid homeostasis. High levels of cholesterol in the liver will lead to increased production of bile acids and subsequent activation of FXR. In response to this activating signal FXR decreases the absorption of cholesterol in the intestine, favoring excretion, increases the clearance and oxidation of triglycerides and decreases the synthesis of fatty acids leading to a reduction in VLDL production.

[0046] The ability of FXR to regulate bile-acid synthesis, clearance and homeostasis as supported by the ability of FXR ligands to promote the transport of bile acid and phospholipids out of the liver suggests a utility for such compounds in diseases of disturbed bile acid and cholesterol flow such as Primary Biliary cirrhosis and NASH. In this regard FXR agonists have been shown to be effective in animal models of cholestasis, gallstones, and liver fibrosis (Liu et al., J Clin Invest 2003, 112(11):1678-87; Fiorocci et al., Gastroenterology 2004, 127(5):1497-512; Fiorocci et al., J Pharmacol Exp Ther 2005, 313(2):604-12; Fiorocci et al., J Pharmacol Exp Ther 2005, 314(2):584-95).

[0047] In some embodiments, compounds disclosed herein are used in the treatment of a disease, disorder or condition in a mammal that would benefit from FXR modulation.

[0048] In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is selected from nonalcoholic steatohepatitis (NASH), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events,

atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis and obesity. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is nonalcoholic steatohepatitis (NASH). In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is hyperlipidemia. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is hypercholesterolemia. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is hypertriglyceridemia. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is dyslipidemia. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is lipodystrophy. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is atherosclerosis. In some embodiments, is a

method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is atherosclerotic disease. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is atherosclerotic cardiovascular disease. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is Syndrome X. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is diabetes mellitus. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is type II diabetes. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is insulin insensitivity. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is hyperglycemia. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of

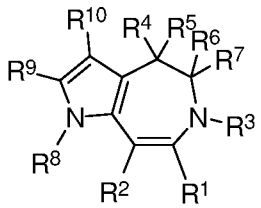
Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is cholestasis. In some embodiments, is a method of treating a disease, disorder or condition in a mammal that would benefit from FXR modulation comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease, disorder or condition in a mammal is obesity.

[0049] In some embodiments, is a method of modulating FXR activity comprising contacting FXR, or portion thereof, with a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, is an FXR agonist. In some embodiments, the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, is an FXR partial agonist.

[0050] In some embodiments, the disease, disorder or condition in a mammal that would benefit from FXR modulation is selected from nonalcoholic steatohepatitis (NASH), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events, atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis and obesity.

Compounds

[0051] In one aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:

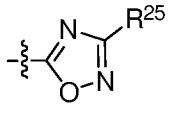
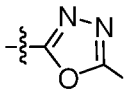


Formula (I);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally

substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)$N(R^{25})R^{26}$,  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^3 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, optionally substituted -(C_1-C_2alkylene)-(heteroaryl), -C(O)R^{20}, -C(O)OR^{20}, -S(O)$_2R^{20}$, -C(O)$N(R^{21})R^{22}$, -C(O)$N(R^{21})$S(O)$_2R^{24}$, -C(O)$N(R^{23})N(R^{21})R^{22}$, -C(O)$N(R^{23})N(R^{21})$S(O)$_2R^{24}$, -$N(R^{23})$C(O)R^{20}, -$N(R^{23})$C(O)$N(R^{21})R^{22}$, -$N(R^{23})$C(O)$N(R^{21})$S(O)$_2R^{24}$, -$N(R^{20})$C(O)$N(R^{23})N(R^{21})R^{22}$, -$N(R^{20})$C(O)$N(R^{23})N(R^{21})$S(O)$_2R^{24}$, -$N(R^{23})$C(O)OR^{20}, -P(O)OR^{20}, and -P(O)(OR^{19})OR^{20};

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7cycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)$N(R^{27})R^{28}$;

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{19}, R^{20}, and R^{23} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{21} and R^{22} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{24} is selected from the group consisting of optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted, aryl optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); and

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring.

[0052] In one embodiment is a compound of Formula (I) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (I) wherein R^4 and R^5 are

each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (I) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (I) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (I) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

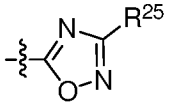
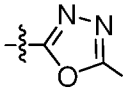
[0053] In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are each hydrogen.

[0054] In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0055] In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0056] In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is

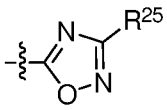
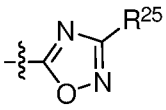
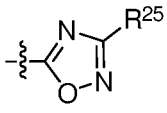
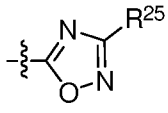
hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (I) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

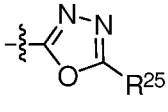
[0057] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -CN.

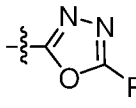
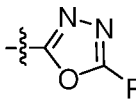
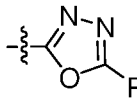
[0058] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[0059] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-

C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[0060] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  , and R^{25} is ethyl.

[0061] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is

a compound of Formula (I) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^2 is  , and R^{25} is ethyl.

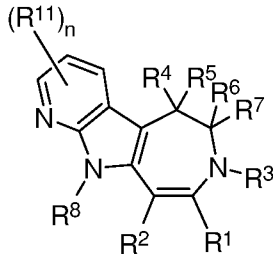
[0062] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[0063] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[0064] In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further

embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^8 is hydrogen.

[0065] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ia);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0066] In one embodiment is a compound of Formula (Ia) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ia) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ia) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a

compound of Formula (Ia) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ia) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

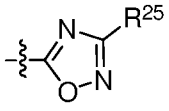
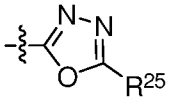
[0067] In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are each hydrogen.

[0068] In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0069] In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0070] In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are

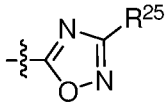
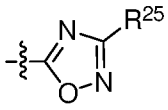
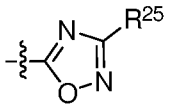
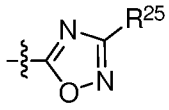
hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ia) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

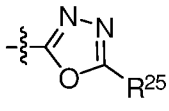
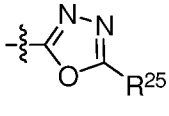
[0071] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -CN.

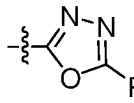
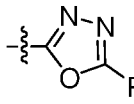
[0072] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[0073] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is -

$C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are ethyl.

[0074] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  , and R^{25} is ethyl.

[0075] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of

Formula (Ia) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^2 is  , and R^{25} is ethyl.

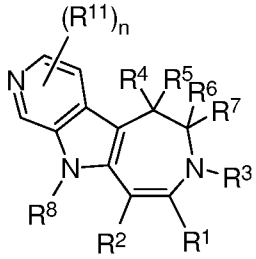
[0076] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[0077] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[0078] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein

R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^8 is hydrogen.

[0079] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ib);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0080] In one embodiment is a compound of Formula (Ib) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ib) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ib) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ib) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ib) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

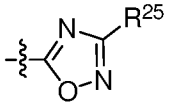
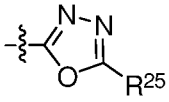
[0081] In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are each hydrogen.

[0082] In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0083] In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0084] In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ib) wherein R^6 and R^7 are

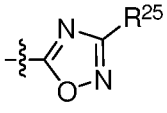
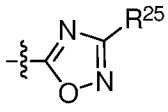
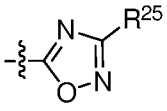
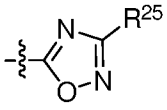
hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

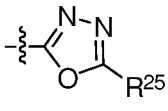
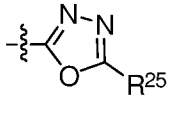
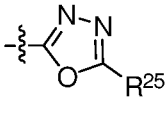
[0085] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -CN.

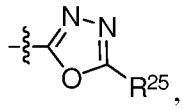
[0086] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[0087] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned

embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[0088] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is ethyl.

[0089] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the

aforementioned embodiments is a compound of Formula (Ib) wherein R^2 is  , and R^{25} is ethyl.

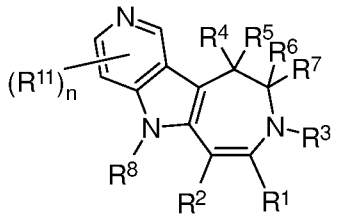
[0090] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[0091] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[0092] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is methyl. In a further embodiment of

the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^8 is hydrogen.

[0093] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ic), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ic);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[0094] In one embodiment is a compound of Formula (Ic) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ic) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ic) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ic) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ic) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

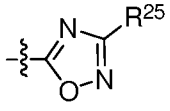
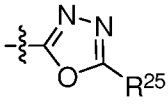
[0095] In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally

substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are each hydrogen.

[0096] In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[0097] In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

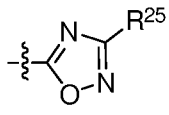
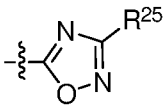
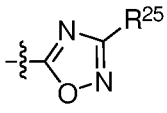
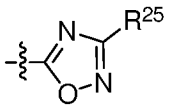
[0098] In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ic) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

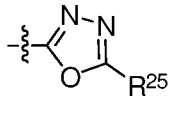
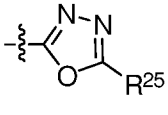
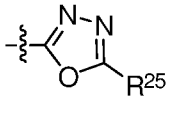
[0099] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, $-C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -CN.

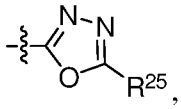
[00100] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00101] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are

hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00102] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is ethyl.

[00103] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is methyl. In a further

embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^2 is  , and R^{25} is ethyl.

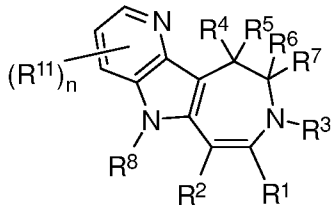
[00104] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00105] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00106] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is methyl. In a further embodiment of

the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^8 is hydrogen.

[00107] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Id), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Id);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[00108] In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Id) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Id) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Id) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00109] In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^6 and

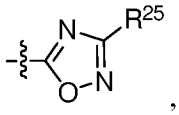
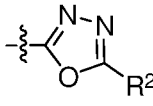
R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are each hydrogen.

[00110] In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00111] In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00112] In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Id) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is $-C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

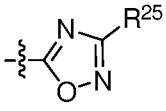
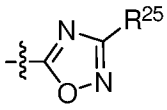
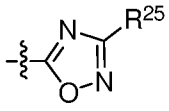
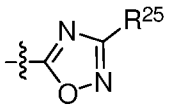
[00113] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, -

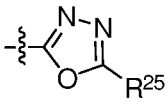
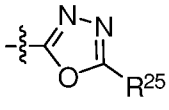
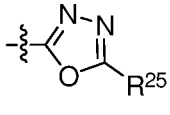
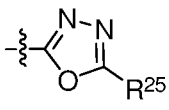
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -CN.

[00114] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00115] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00116] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is ethyl.

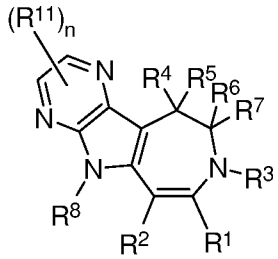
[00117] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^2 is  , and R^{25} is ethyl.

[00118] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00119] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00120] In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Id) wherein R^8 is hydrogen.

[00121] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ie), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ie);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00122] In one embodiment is a compound of Formula (Ie) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ie) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ie) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ie) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ie) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00123] In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^6 and

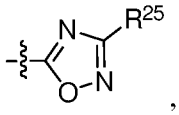
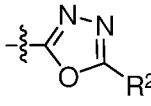
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are each hydrogen.

[00124] In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00125] In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00126] In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ie) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

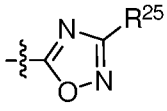
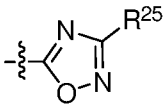
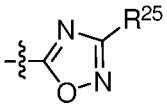
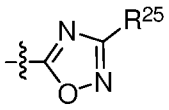
[00127] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is selected from the group consisting of -CN, -$C(O)OR^{25}$, -

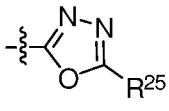
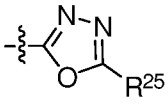
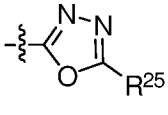
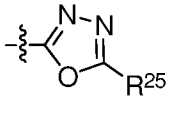
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -CN.

[00128] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00129] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00130] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is ethyl.

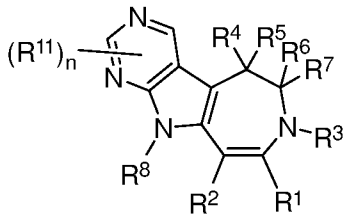
[00131] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^2 is  , and R^{25} is ethyl.

[00132] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00133] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00134] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ie) wherein R^8 is hydrogen.

[00135] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (If), or a pharmaceutically acceptable salt or solvate thereof:



Formula (If);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00136] In one embodiment is a compound of Formula (If) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (If) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (If) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (If) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (If) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00137] In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^6 and

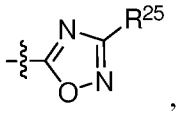
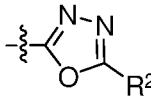
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are each hydrogen.

[00138] In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl.

[00139] In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00140] In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (If) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

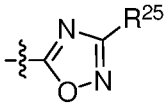
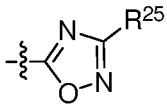
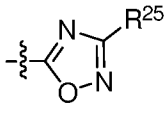
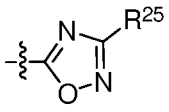
[00141] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -

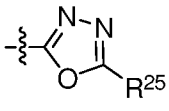
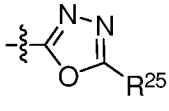
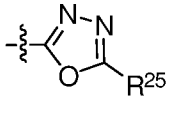
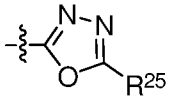
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -CN.

[00142] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00143] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00144] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is ethyl.

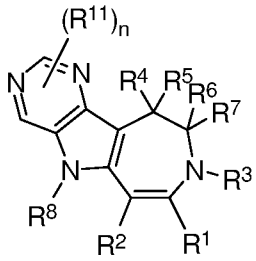
[00145] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^2 is  , and R^{25} is ethyl.

[00146] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00147] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00148] In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (If) wherein R^8 is hydrogen.

[00149] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ig), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ig);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00150] In one embodiment is a compound of Formula (Ig) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ig) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ig) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ig) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ig) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00151] In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^6 and

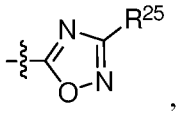
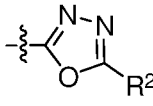
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are each hydrogen.

[00152] In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl.

[00153] In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00154] In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ig) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

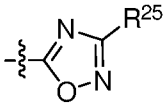
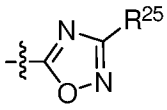
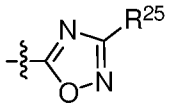
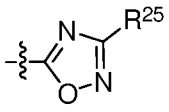
[00155] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -

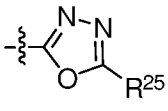
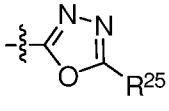
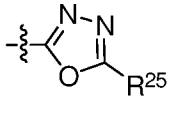
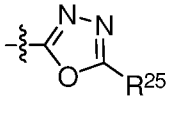
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -CN.

[00156] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00157] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00158] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is ethyl.

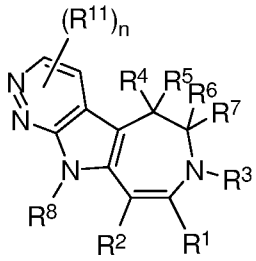
[00159] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^2 is  , and R^{25} is ethyl.

[00160] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00161] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00162] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ig) wherein R^8 is hydrogen.

[00163] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ih), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ih);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00164] In one embodiment is a compound of Formula (Ih) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ih) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ih) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ih) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ih) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00165] In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^6 and

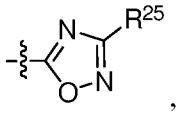
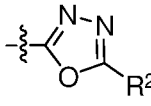
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are each hydrogen.

[00166] In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00167] In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$S(O)_2R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00168] In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ih) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -$C(O)N(R^{21})R^{22}$, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

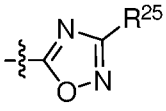
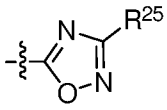
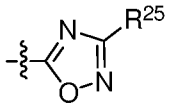
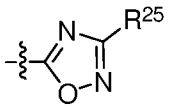
[00169] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is selected from the group consisting of -CN, -$C(O)OR^{25}$, -

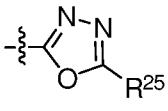
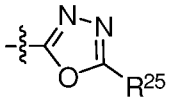
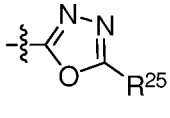
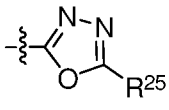
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -CN.

[00170] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00171] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00172] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is ethyl.

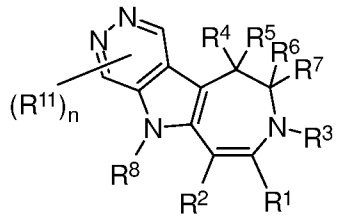
[00173] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^2 is  , and R^{25} is ethyl.

[00174] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00175] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00176] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ih) wherein R^8 is hydrogen.

[00177] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ii), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ii);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00178] In one embodiment is a compound of Formula (Ii) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ii) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ii) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ii) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ii) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00179] In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^6 and

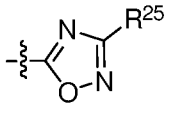
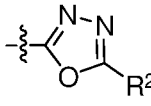
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are each hydrogen.

[00180] In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl.

[00181] In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00182] In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ii) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

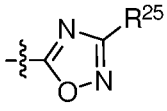
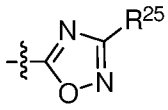
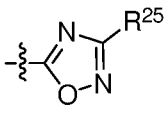
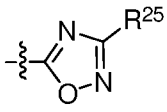
[00183] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -

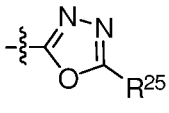
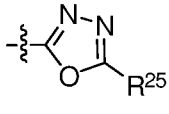
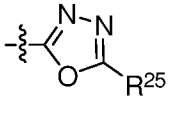
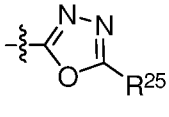
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -CN.

[00184] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00185] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00186] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is ethyl.

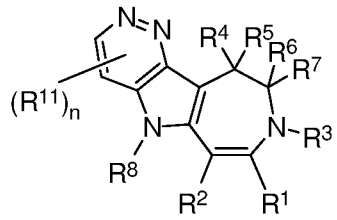
[00187] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^2 is  , and R^{25} is ethyl.

[00188] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00189] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00190] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ii) wherein R^8 is hydrogen.

[00191] In some embodiments provided herein, the compound of Formula (I) has the structure of Formula (Ii), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ij);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00192] In one embodiment is a compound of Formula (Ij) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (Ij) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (Ij) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (Ij) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (Ij) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00193] In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^6 and

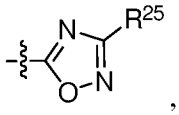
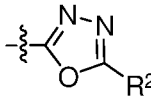
R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are each hydrogen.

[00194] In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)R^{20}, and R^{20} is optionally substituted heteroaryl.

[00195] In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -S(O)$_2$$R^{20}$, and R^{20} is optionally substituted heteroaryl.

[00196] In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are independently optionally substituted C_1-C_6alkyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted aryl. In another embodiment is a compound of Formula (Ij) wherein R^6 and R^7 are hydrogen, R^4 and R^5 are methyl, R^3 is -C(O)N(R^{21})R^{22}, R^{21} is hydrogen and R^{22} is optionally substituted heteroaryl.

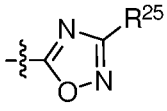
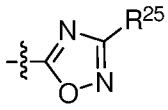
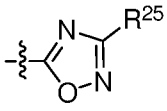
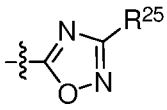
[00197] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -

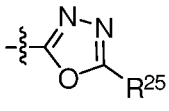
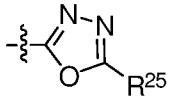
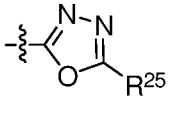
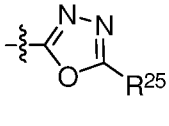
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -CN.

[00198] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00199] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00200] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is ethyl.

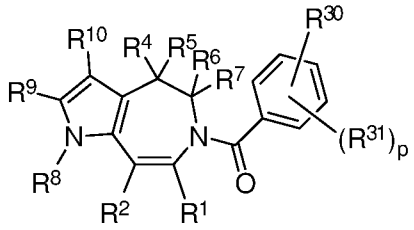
[00201] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^2 is  , and R^{25} is ethyl.

[00202] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00203] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00204] In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (Ij) wherein R^8 is hydrogen.

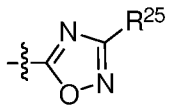
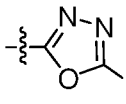
[00205] In yet another aspect, provided herein is a compound having the structure of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

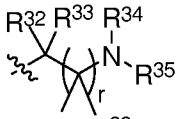
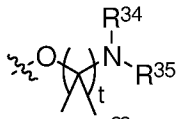
R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -

(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen,  , or  ;

each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

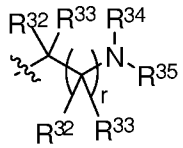
[00206] In one embodiment is a compound of Formula (II) wherein p is 0. In another embodiment is a compound of Formula (II) wherein p is 1. In another embodiment is a compound of Formula (II) wherein p is 2. In another embodiment is a compound of Formula (II) wherein p is 3. In another embodiment is a compound of Formula (II) wherein p is 4.

[00207] In another embodiment is a compound of Formula (II) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein p is 2 and each R^{31} is F.

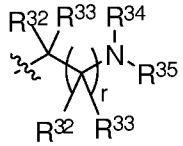
[00208] In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 2 and each R^{31} is F.

[00209] In another embodiment is a compound of Formula (II) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein p is 1 and R^{31} is F.

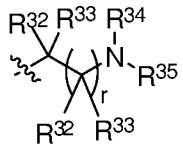
[00210] In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is F, p is 1 and R^{31} is F.



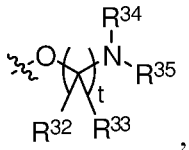
[00211] In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 2 and each R^{31} is F.

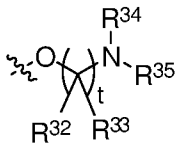
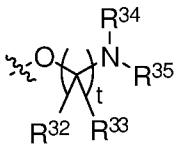
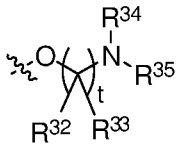


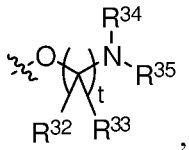
[00212] In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 1 and R^{31} is F.

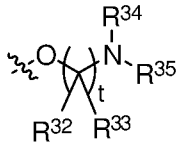


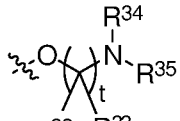
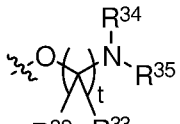
[00213] In another embodiment is a compound of Formula (II) wherein R^{30} is , and p is 0.

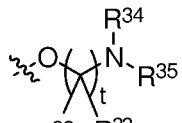


[00214] In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00215] In another embodiment is a compound of Formula (II) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (II) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of

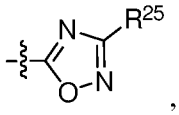
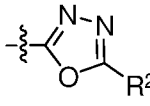
Formula (II) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (II) wherein R^{30} is  , p is 1 and R^{31} is F.

[00216] In another embodiment is a compound of Formula (II) wherein R^{30} is  , and p is 0.

[00217] In another embodiment is a compound of Formula (II) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (II) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (II) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (II) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (II) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00218] In another embodiment is a compound of Formula (II) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (II) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (II) wherein R^6 and R^7 are each hydrogen.

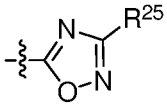
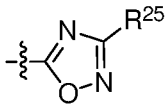
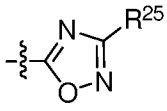
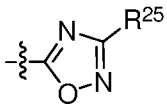
[00219] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -

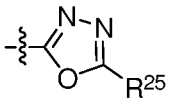
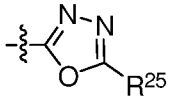
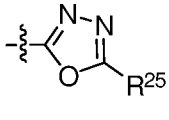
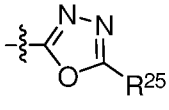
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -CN.

[00220] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00221] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00222] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is ethyl.

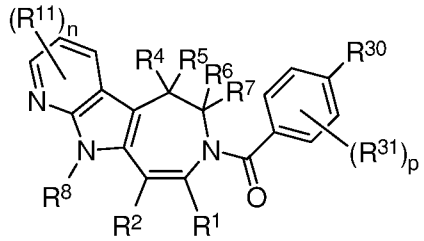
[00223] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^2 is  , and R^{25} is ethyl.

[00224] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00225] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00226] In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (II) wherein R^8 is hydrogen.

[00227] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[00228] In one embodiment is a compound of Formula (IIa) wherein p is 0. In another embodiment is a compound of Formula (IIa) wherein p is 1. In another embodiment is a compound of Formula (IIa) wherein p is 2. In another embodiment is a compound of Formula (IIa) wherein p is 3. In another embodiment is a compound of Formula (IIa) wherein p is 4.

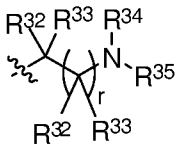
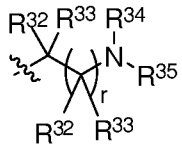
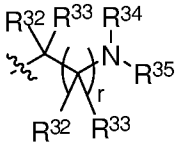
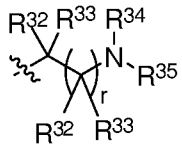
[00229] In another embodiment is a compound of Formula (IIa) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein p is 2 and each R^{31} is F.

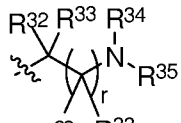
[00230] In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a

compound of Formula (IIa) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 2 and each R^{31} is F.

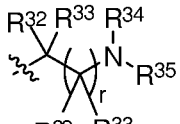
[00231] In another embodiment is a compound of Formula (IIa) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein p is 1 and R^{31} is F.

[00232] In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein R^{30} is F, p is 1 and R^{31} is F.

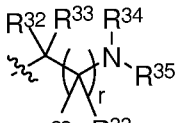
[00233] In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 2 and each R^{31} is F.



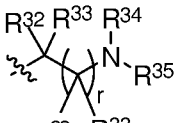
[00234] In another embodiment is a compound of Formula (IIa) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another



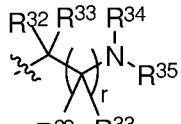
embodiment is a compound of Formula (IIa) wherein R^{30} is , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of



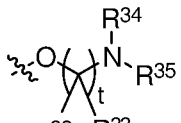
Formula (IIa) wherein R^{30} is , p is 1 and R^{31} is halogen. In another embodiment is



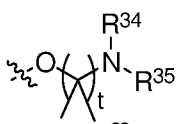
a compound of Formula (IIa) wherein R^{30} is , p is 1 and R^{31} is F.



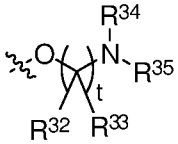
[00235] In another embodiment is a compound of Formula (IIa) wherein R^{30} is , and p is 0.



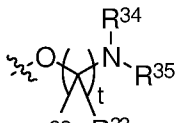
[00236] In another embodiment is a compound of Formula (IIa) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In

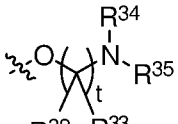
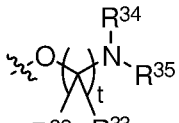
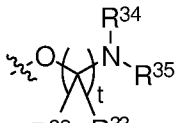
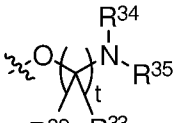


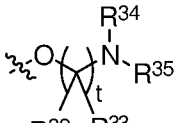
another embodiment is a compound of Formula (IIa) wherein R^{30} is , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment



is a compound of Formula (IIa) wherein R^{30} is , p is 2 and each R^{31} is halogen. In

another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00237] In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIa) wherein R^{30} is  , p is 1 and R^{31} is F.



[00238] In another embodiment is a compound of Formula (IIa) wherein R^{30} is , and p is 0.

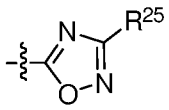
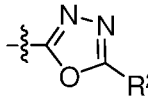
[00239] In another embodiment is a compound of Formula (IIa) wherein n is 0. In another embodiment is a compound of Formula (IIa) wherein n is 1. In another embodiment is a compound of Formula (IIa) wherein n is 2. In another embodiment is a compound of Formula (IIa) wherein n is 3.

[00240] In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIa) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In

another embodiment is a compound of Formula (IIa) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00241] In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIa) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIa) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIa) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

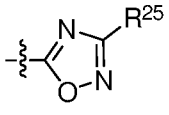
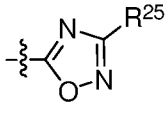
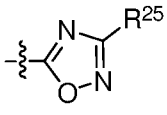
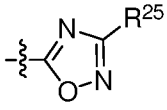
[00242] In another embodiment is a compound of Formula (IIa) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIa) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIa) wherein R^6 and R^7 are each hydrogen.

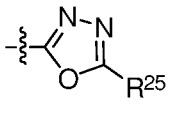
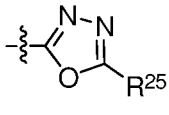
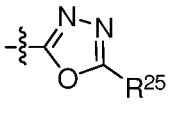
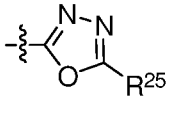
[00243] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -CN.

[00244] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted

heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00245] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00246] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is ethyl.

[00247] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^2 is  , and R^{25} is ethyl.

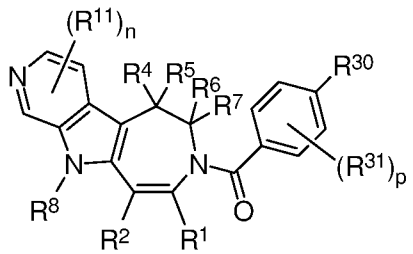
[00248] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is methyl. In a further embodiment of

the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00249] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00250] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIa) wherein R^8 is hydrogen.

[00251] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIb);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

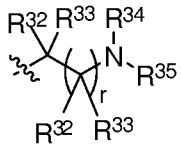
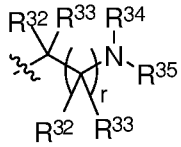
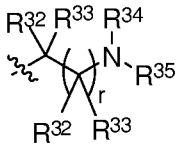
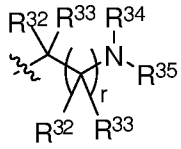
[00252] In one embodiment is a compound of Formula (IIb) wherein p is 0. In another embodiment is a compound of Formula (IIb) wherein p is 1. In another embodiment is a compound of Formula (IIb) wherein p is 2. In another embodiment is a compound of Formula (IIb) wherein p is 3. In another embodiment is a compound of Formula (IIb) wherein p is 4.

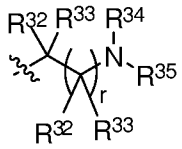
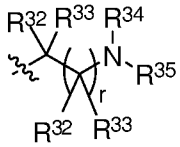
[00253] In another embodiment is a compound of Formula (IIb) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein p is 2 and each R^{31} is F.

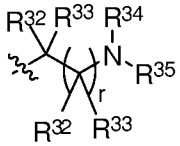
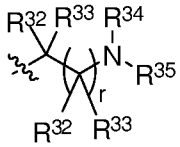
[00254] In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 2 and each R^{31} is F.

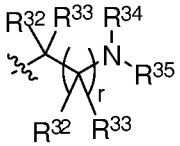
[00255] In another embodiment is a compound of Formula (IIb) wherein p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein p is 1 and R^{31} is F.

[00256] In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is F, p is 1 and R^{31} is F.

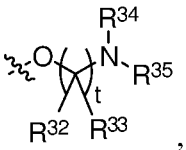
[00257] In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is F.

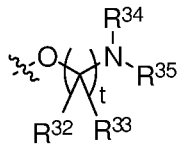
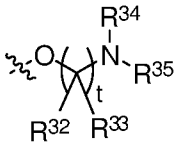
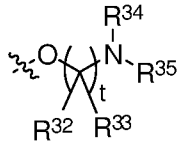
[00258] In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is

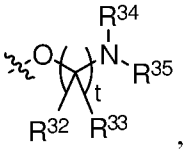
halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is F.



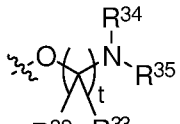
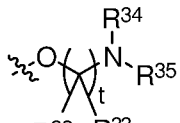
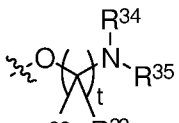
[00259] In another embodiment is a compound of Formula (IIb) wherein R^{30} is , and p is 0.

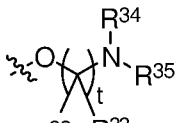


[00260] In another embodiment is a compound of Formula (IIb) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00261] In another embodiment is a compound of Formula (IIb) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-

C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIb) wherein R^{30} is  , p is 1 and R^{31} is F.



[00262] In another embodiment is a compound of Formula (IIb) wherein R^{30} is , and p is 0.

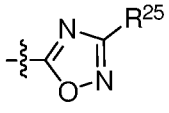
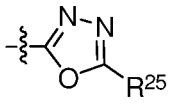
[00263] In another embodiment is a compound of Formula (IIb) wherein n is 0. In another embodiment is a compound of Formula (IIb) wherein n is 1. In another embodiment is a compound of Formula (IIb) wherein n is 2. In another embodiment is a compound of Formula (IIb) wherein n is 3.

[00264] In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIb) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIb) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00265] In another embodiment is a compound of Formula (IIb) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIb) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a

compound of Formula (IIb) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIb) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIb) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIb) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

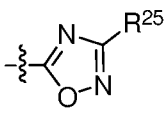
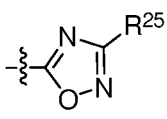
[00266] In another embodiment is a compound of Formula (IIb) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIb) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIb) wherein R^6 and R^7 are each hydrogen.

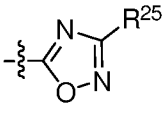
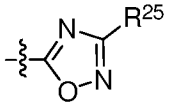
[00267] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -CN.

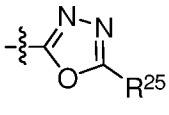
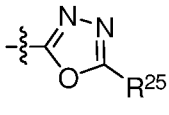
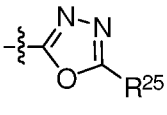
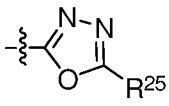
[00268] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of

Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00269] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00270] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a

compound of Formula (IIb) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  , and R^{25} is ethyl.

[00271] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^2 is  , and R^{25} is ethyl.

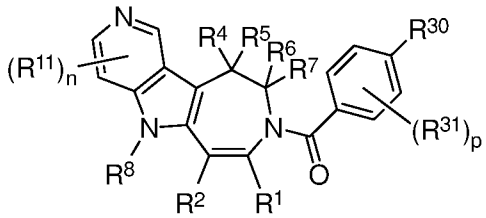
[00272] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00273] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula

(IIb) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00274] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIb) wherein R^8 is hydrogen.

[00275] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIc), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIc);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

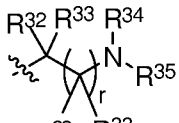
[00276] In one embodiment is a compound of Formula (IIc) wherein p is 0. In another embodiment is a compound of Formula (IIc) wherein p is 1. In another embodiment is a compound of Formula (IIc) wherein p is 2. In another embodiment is a compound of Formula (IIc) wherein p is 3. In another embodiment is a compound of Formula (IIc) wherein p is 4.

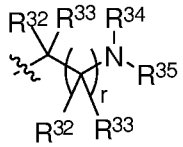
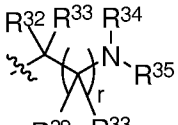
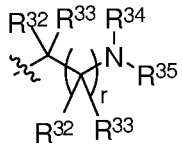
[00277] In another embodiment is a compound of Formula (IIc) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein p is 2 and each R^{31} is F.

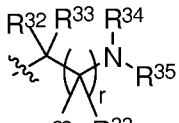
[00278] In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 2 and each R^{31} is F.

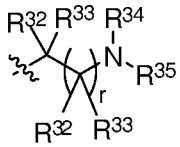
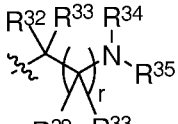
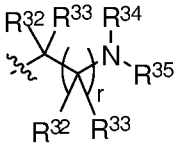
[00279] In another embodiment is a compound of Formula (IIc) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein p is 1 and R^{31} is F.

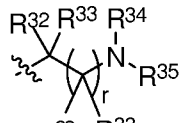
[00280] In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is F, p is 1 and R^{31} is F.

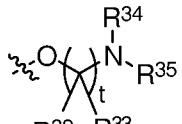
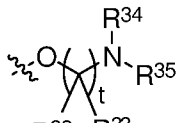
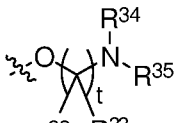
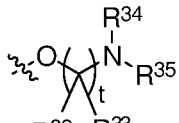


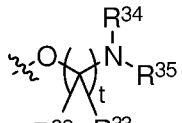
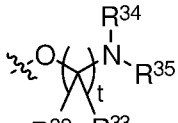
[00281] In another embodiment is a compound of Formula (IIc) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is F.

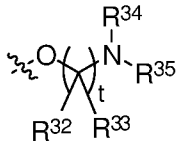
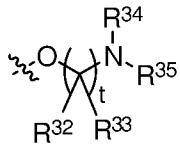


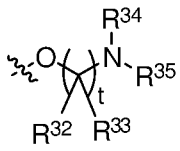
[00282] In another embodiment is a compound of Formula (IIc) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is F.

[00283] In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , and p is 0.

[00284] In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00285] In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of

Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIc) wherein R^{30} is  , p is 1 and R^{31} is F.



[00286] In another embodiment is a compound of Formula (IIc) wherein R^{30} is , and p is 0.

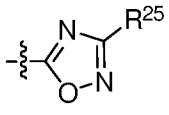
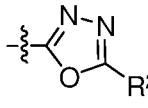
[00287] In another embodiment is a compound of Formula (IIc) wherein n is 0. In another embodiment is a compound of Formula (IIc) wherein n is 1. In another embodiment is a compound of Formula (IIc) wherein n is 2. In another embodiment is a compound of Formula (IIc) wherein n is 3.

[00288] In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIc) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIc) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00289] In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIc) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIc) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl

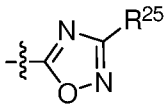
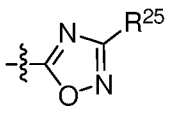
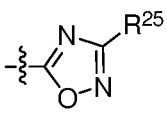
ring. In some embodiments is a compound of Formula (IIc) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

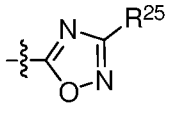
[00290] In another embodiment is a compound of Formula (IIc) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIc) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIc) wherein R^6 and R^7 are each hydrogen.

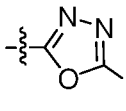
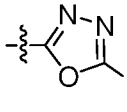
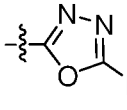
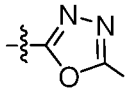
[00291] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -CN.

[00292] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00293] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are ethyl.

[00294] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is methyl. In a further

embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is ethyl.

[00295] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^2 is  , and R^{25} is ethyl.

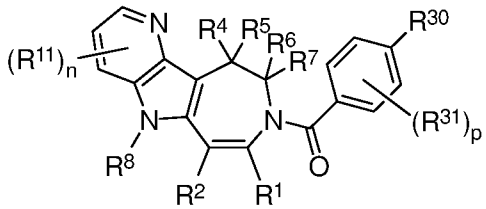
[00296] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00297] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the

aforementioned embodiments is a compound of Formula (IIc) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00298] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIc) wherein R^8 is hydrogen.

[00299] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IId), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IId);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

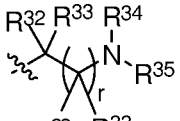
[00300] In one embodiment is a compound of Formula (IId) wherein p is 0. In another embodiment is a compound of Formula (IId) wherein p is 1. In another embodiment is a compound of Formula (IId) wherein p is 2. In another embodiment is a compound of Formula (IId) wherein p is 3. In another embodiment is a compound of Formula (IId) wherein p is 4.

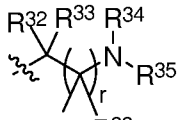
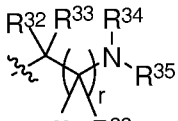
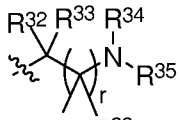
[00301] In another embodiment is a compound of Formula (IId) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein p is 2 and each R^{31} is F.

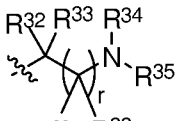
[00302] In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 2 and each R^{31} is F.

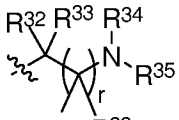
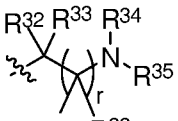
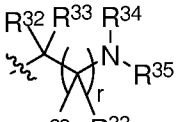
[00303] In another embodiment is a compound of Formula (IId) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein p is 1 and R^{31} is F.

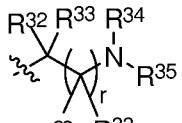
[00304] In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is F, p is 1 and R^{31} is F.



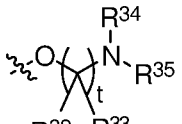
[00305] In another embodiment is a compound of Formula (IId) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is F.

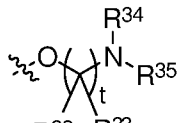
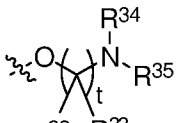
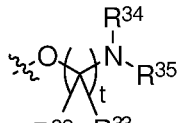


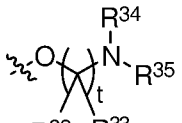
[00306] In another embodiment is a compound of Formula (IId) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is F.

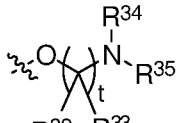


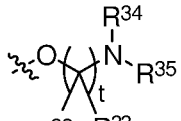
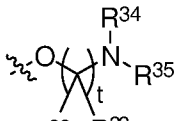
[00307] In another embodiment is a compound of Formula (IId) wherein R^{30} is , and p is 0.

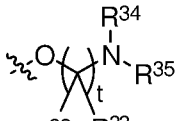


[00308] In another embodiment is a compound of Formula (IId) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00309] In another embodiment is a compound of Formula (IId) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of

Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IId) wherein R^{30} is  , p is 1 and R^{31} is F.



[00310] In another embodiment is a compound of Formula (IId) wherein R^{30} is , and p is 0.

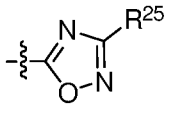
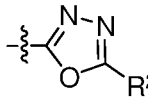
[00311] In another embodiment is a compound of Formula (IId) wherein n is 0. In another embodiment is a compound of Formula (IId) wherein n is 1. In another embodiment is a compound of Formula (IId) wherein n is 2. In another embodiment is a compound of Formula (IId) wherein n is 3.

[00312] In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IId) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IId) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00313] In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IId) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IId) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl

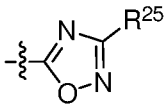
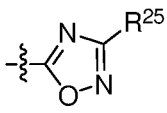
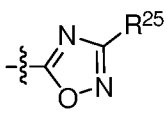
ring. In some embodiments is a compound of Formula (IId) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

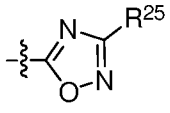
[00314] In another embodiment is a compound of Formula (IId) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IId) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IId) wherein R^6 and R^7 are each hydrogen.

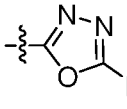
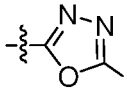
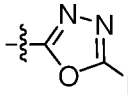
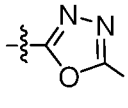
[00315] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -CN.

[00316] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00317] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00318] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is methyl. In a further

embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is ethyl.

[00319] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^2 is  , and R^{25} is ethyl.

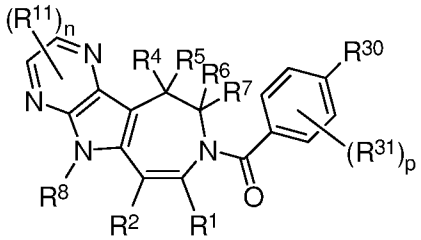
[00320] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00321] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the

aforementioned embodiments is a compound of Formula (IId) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00322] In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IId) wherein R^8 is hydrogen.

[00323] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIe), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIe);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00324] In one embodiment is a compound of Formula (IIe) wherein p is 0. In another embodiment is a compound of Formula (IIe) wherein p is 1. In another embodiment is a

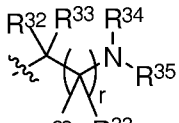
compound of Formula (IIe) wherein p is 2. In another embodiment is a compound of Formula (IIe) wherein p is 3. In another embodiment is a compound of Formula (IIe) wherein p is 4.

[00325] In another embodiment is a compound of Formula (IIe) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein p is 2 and each R^{31} is F.

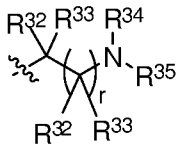
[00326] In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 2 and each R^{31} is F.

[00327] In another embodiment is a compound of Formula (IIe) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein p is 1 and R^{31} is F.

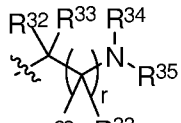
[00328] In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is F, p is 1 and R^{31} is F.



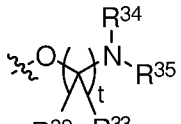
[00329] In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 2 and each R^{31} is F.

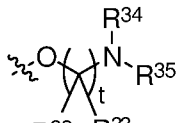
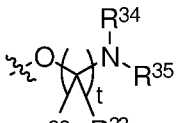
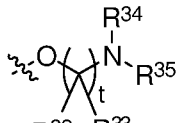


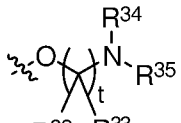
[00330] In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 1 and R^{31} is F.

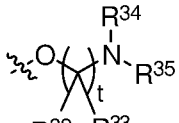


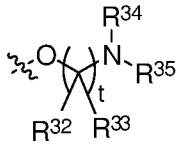
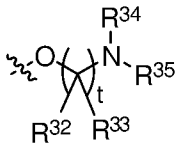
[00331] In another embodiment is a compound of Formula (IIe) wherein R^{30} is , and p is 0.

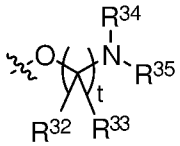


[00332] In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00333] In another embodiment is a compound of Formula (IIe) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of

Formula (IIe) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , p is 1 and R^{31} is F.

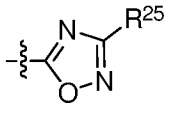
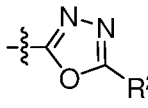
[00334] In another embodiment is a compound of Formula (IIe) wherein R^{30} is  , and p is 0.

[00335] In another embodiment is a compound of Formula (IIe) wherein n is 0. In another embodiment is a compound of Formula (IIe) wherein n is 1. In another embodiment is a compound of Formula (IIe) wherein n is 2.

[00336] In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIe) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIe) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00337] In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIe) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIe) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIe) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

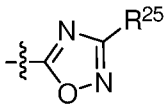
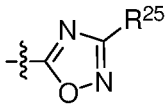
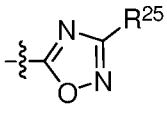
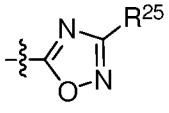
[00338] In another embodiment is a compound of Formula (IIe) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIe) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIe) wherein R^6 and R^7 are each hydrogen.

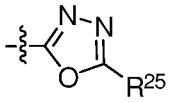
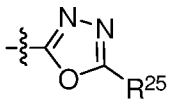
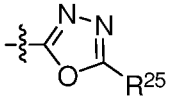
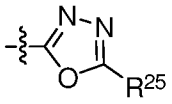
[00339] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -CN.

[00340] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00341] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are

each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00342] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is ethyl.

[00343] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^2 is  , and R^{25} is ethyl.

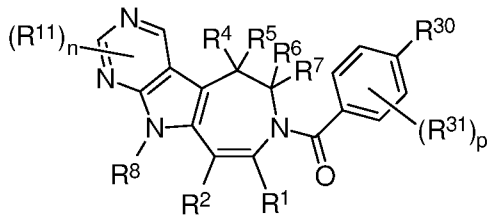
[00344] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00345] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00346] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is selected from the group consisting of hydrogen, optionally

substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIe) wherein R^8 is hydrogen.

[00347] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIf), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIf);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

[00348] In one embodiment is a compound of Formula (IIf) wherein p is 0. In another embodiment is a compound of Formula (IIf) wherein p is 1. In another embodiment is a compound of Formula (IIf) wherein p is 2. In another embodiment is a compound of Formula (IIf) wherein p is 3. In another embodiment is a compound of Formula (IIf) wherein p is 4.

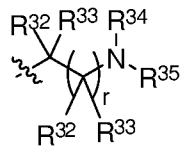
[00349] In another embodiment is a compound of Formula (IIf) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-

C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein p is 2 and each R^{31} is F.

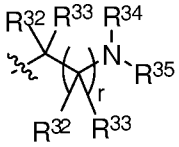
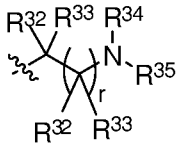
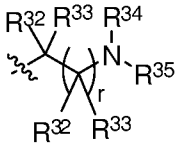
[00350] In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 2 and each R^{31} is F.

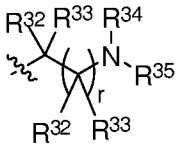
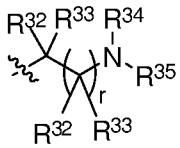
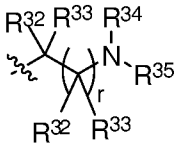
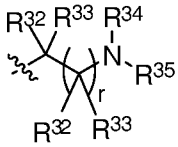
[00351] In another embodiment is a compound of Formula (IIf) wherein p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein p is 1 and R^{31} is F.

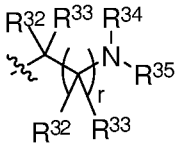
[00352] In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is F, p is 1 and R^{31} is F.

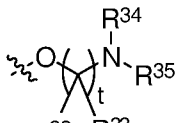
[00353] In another embodiment is a compound of Formula (IIf) wherein R^{30} is 

, p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In

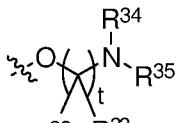
another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00354] In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , p is 1 and R^{31} is F.

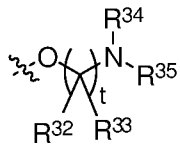
[00355] In another embodiment is a compound of Formula (IIf) wherein R^{30} is  , and p is 0.



[00356] In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 2 and each R^{31} is F.



[00357] In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIf) wherein R^{30} is , p is 1 and R^{31} is F.

[00358] In another embodiment is a compound of Formula (IIf) wherein R^{30} is 

, and p is 0.

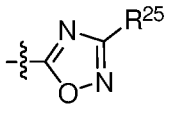
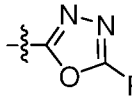
[00359] In another embodiment is a compound of Formula (IIf) wherein n is 0. In another embodiment is a compound of Formula (IIf) wherein n is 1. In another embodiment is a compound of Formula (IIf) wherein n is 2. In another embodiment is a compound of Formula (IIf) wherein n is 3.

[00360] In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIf) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIf) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00361] In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIf) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIf) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIf) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00362] In another embodiment is a compound of Formula (IIf) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIf) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a

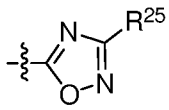
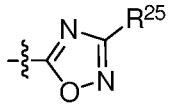
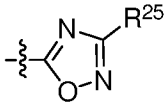
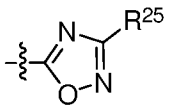
compound of Formula (IIf) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIf) wherein R^6 and R^7 are each hydrogen.

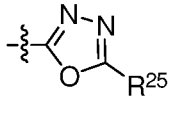
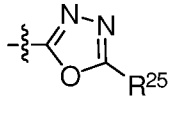
[00363] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is selected from the group consisting of -CN, -$C(O)OR^{25}$, -$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -CN.

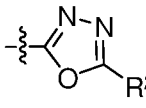
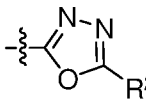
[00364] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)OR^{25}$, and R^{25} is ethyl.

[00365] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -$C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of

hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00366] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  , and R^{25} is ethyl.

[00367] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a

compound of Formula (IIf) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^2 is  , and R^{25} is ethyl.

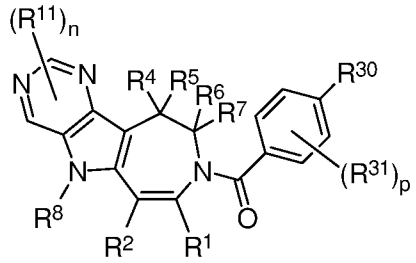
[00368] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00369] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00370] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of

Formula (IIf) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIf) wherein R^8 is hydrogen.

[00371] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIg), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIg);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

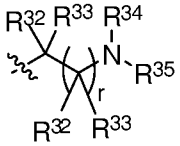
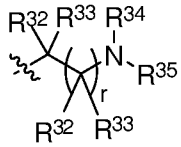
[00372] In one embodiment is a compound of Formula (IIg) wherein p is 0. In another embodiment is a compound of Formula (IIg) wherein p is 1. In another embodiment is a compound of Formula (IIg) wherein p is 2. In another embodiment is a compound of Formula (IIg) wherein p is 3. In another embodiment is a compound of Formula (IIg) wherein p is 4.

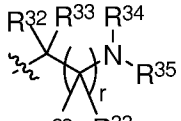
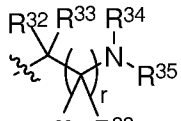
[00373] In another embodiment is a compound of Formula (IIg) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein p is 2 and each R^{31} is F.

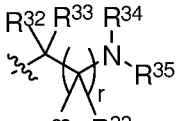
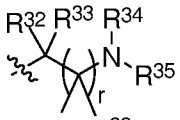
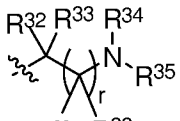
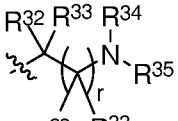
[00374] In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 2 and each R^{31} is F.

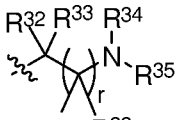
[00375] In another embodiment is a compound of Formula (IIg) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein p is 1 and R^{31} is F.

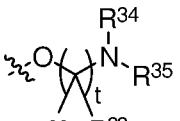
[00376] In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is F, p is 1 and R^{31} is F.

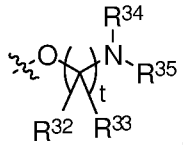
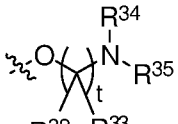
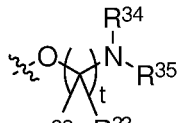
[00377] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment

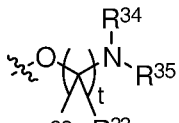
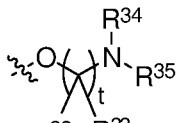
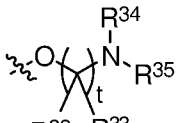
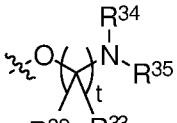
is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is F.

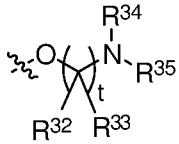
[00378] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is F.

[00379] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , and p is 0.

[00380] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In

another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00381] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , p is 1 and R^{31} is F.

[00382] In another embodiment is a compound of Formula (IIg) wherein R^{30} is  , and p is 0.

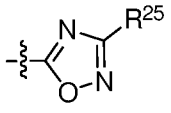
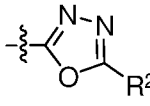
[00383] In another embodiment is a compound of Formula (IIg) wherein n is 0. In another embodiment is a compound of Formula (IIg) wherein n is 1. In another embodiment is a compound of Formula (IIg) wherein n is 2.

[00384] In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIg) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIg) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00385] In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIg) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIg) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIg) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00386] In another embodiment is a compound of Formula (IIg) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIg) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIg) wherein R^6 and R^7 are each hydrogen.

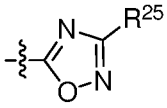
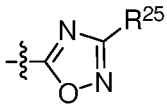
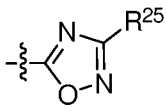
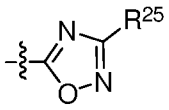
[00387] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, -

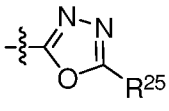
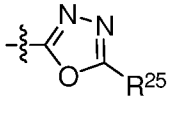
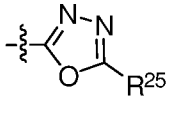
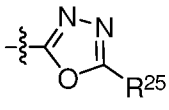
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -CN.

[00388] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00389] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00390] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is ethyl.

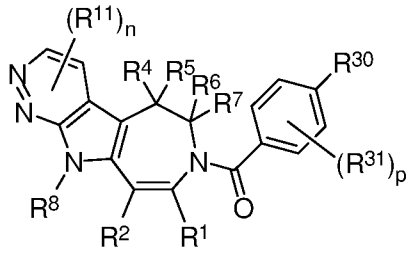
[00391] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^2 is  , and R^{25} is ethyl.

[00392] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00393] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00394] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIg) wherein R^8 is hydrogen.

[00395] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIh), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIh);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[00396] In one embodiment is a compound of Formula (IIh) wherein p is 0. In another embodiment is a compound of Formula (IIh) wherein p is 1. In another embodiment is a compound of Formula (IIh) wherein p is 2. In another embodiment is a compound of Formula (IIh) wherein p is 3. In another embodiment is a compound of Formula (IIh) wherein p is 4.

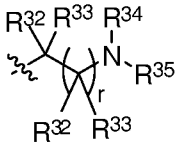
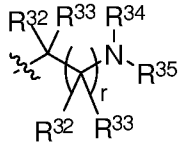
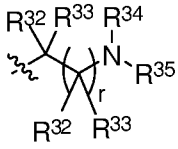
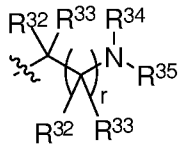
[00397] In another embodiment is a compound of Formula (IIh) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein p is 2 and each R^{31} is F.

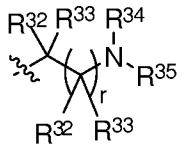
[00398] In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a

compound of Formula (IIh) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 2 and each R^{31} is F.

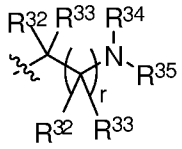
[00399] In another embodiment is a compound of Formula (IIh) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein p is 1 and R^{31} is F.

[00400] In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein R^{30} is F, p is 1 and R^{31} is F.

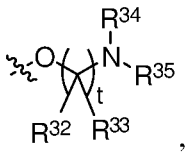
[00401] In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 2 and each R^{31} is F.



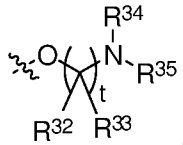
[00402] In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 1 and R^{31} is F.

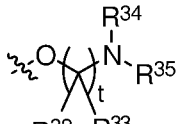
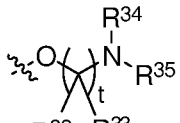
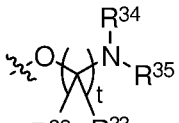
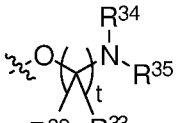


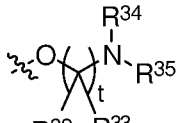
[00403] In another embodiment is a compound of Formula (IIh) wherein R^{30} is , and p is 0.



[00404] In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is , p is 2 and each R^{31} is halogen. In

another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00405] In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , p is 1 and R^{31} is F.

[00406] In another embodiment is a compound of Formula (IIh) wherein R^{30} is  , and p is 0.

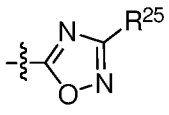
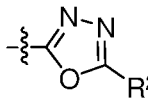
[00407] In another embodiment is a compound of Formula (IIh) wherein n is 0. In another embodiment is a compound of Formula (IIh) wherein n is 1. In another embodiment is a compound of Formula (IIh) wherein n is 2.

[00408] In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIh) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In

another embodiment is a compound of Formula (IIh) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00409] In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIh) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIh) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIh) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

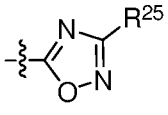
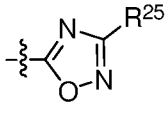
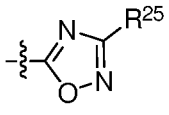
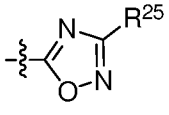
[00410] In another embodiment is a compound of Formula (IIh) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIh) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIh) wherein R^6 and R^7 are each hydrogen.

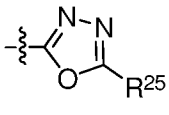
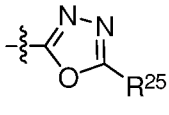
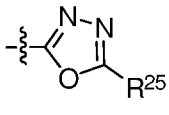
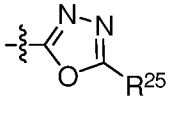
[00411] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -CN.

[00412] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted

heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00413] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00414] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is ethyl.

[00415] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^2 is  , and R^{25} is ethyl.

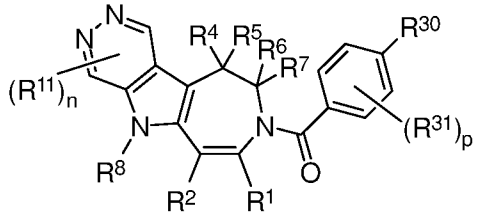
[00416] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is methyl. In a further embodiment of

the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00417] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00418] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIh) wherein R^8 is hydrogen.

[00419] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIi), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIi);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

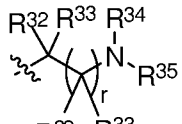
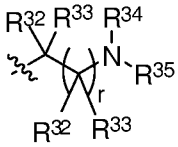
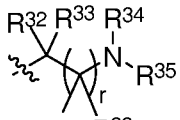
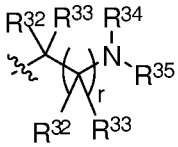
[00420] In one embodiment is a compound of Formula (IIi) wherein p is 0. In another embodiment is a compound of Formula (IIi) wherein p is 1. In another embodiment is a compound of Formula (IIi) wherein p is 2. In another embodiment is a compound of Formula (IIi) wherein p is 3. In another embodiment is a compound of Formula (IIi) wherein p is 4.

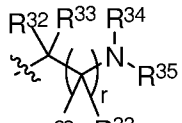
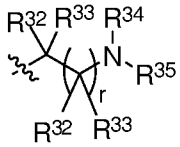
[00421] In another embodiment is a compound of Formula (IIi) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein p is 2 and each R^{31} is F.

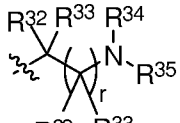
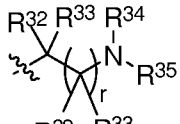
[00422] In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 2 and each R^{31} is F.

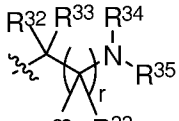
[00423] In another embodiment is a compound of Formula (IIi) wherein p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein p is 1 and R^{31} is F.

[00424] In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is F, p is 1 and R^{31} is F.

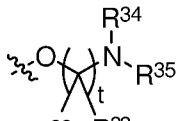
[00425] In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is F.

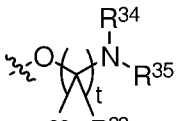
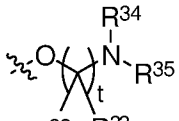
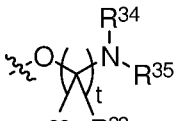
[00426] In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is

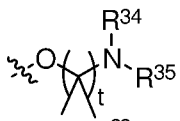
halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is F.



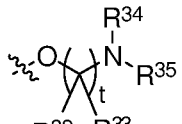
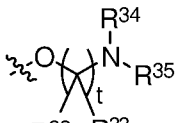
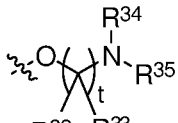
[00427] In another embodiment is a compound of Formula (IIi) wherein R^{30} is , and p is 0.

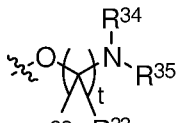


[00428] In another embodiment is a compound of Formula (IIi) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00429] In another embodiment is a compound of Formula (IIi) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-

C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , p is 1 and R^{31} is F.

[00430] In another embodiment is a compound of Formula (IIi) wherein R^{30} is  , and p is 0.

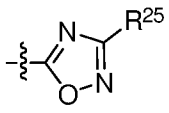
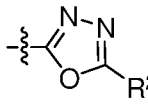
[00431] In another embodiment is a compound of Formula (IIi) wherein n is 0. In another embodiment is a compound of Formula (IIi) wherein n is 1. In another embodiment is a compound of Formula (IIi) wherein n is 2.

[00432] In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIi) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIi) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00433] In another embodiment is a compound of Formula (IIi) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIi) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^4 and R^5 are each methyl. In another embodiment is a

compound of Formula (IIi) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIi) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIi) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

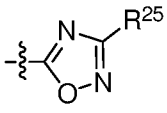
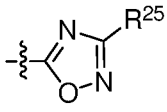
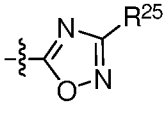
[00434] In another embodiment is a compound of Formula (IIi) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIi) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIi) wherein R^6 and R^7 are each hydrogen.

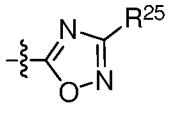
[00435] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -CN.

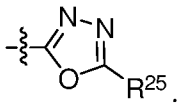
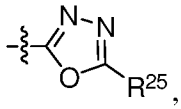
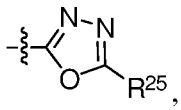
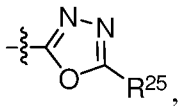
[00436] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the

aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00437] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00438] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is methyl. In a further

embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is ethyl.

[00439] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^2 is  , and R^{25} is ethyl.

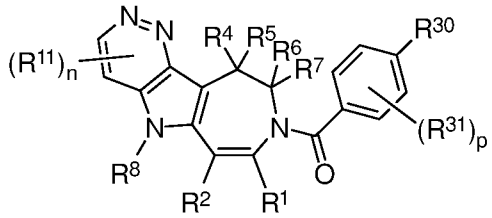
[00440] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00441] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned

embodiments is a compound of Formula (IIi) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00442] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIi) wherein R^8 is hydrogen.

[00443] In some embodiments provided herein, the compound of Formula (II) has the structure of Formula (IIj), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIj);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

[00444] In one embodiment is a compound of Formula (IIj) wherein p is 0. In another embodiment is a compound of Formula (IIj) wherein p is 1. In another embodiment is a

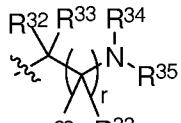
compound of Formula (IIj) wherein p is 2. In another embodiment is a compound of Formula (IIj) wherein p is 3. In another embodiment is a compound of Formula (IIj) wherein p is 4.

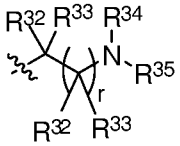
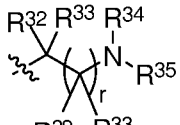
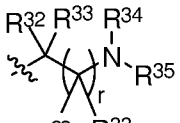
[00445] In another embodiment is a compound of Formula (IIj) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein p is 2 and each R^{31} is F.

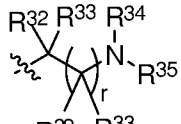
[00446] In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 2 and each R^{31} is F.

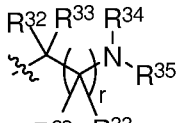
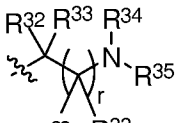
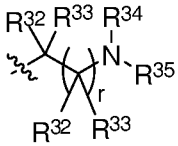
[00447] In another embodiment is a compound of Formula (IIj) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein p is 1 and R^{31} is F.

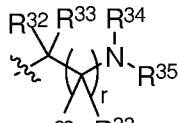
[00448] In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is F, p is 1 and R^{31} is F.

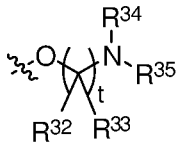
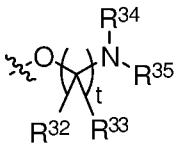
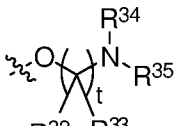
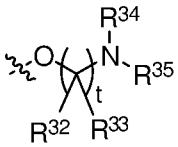


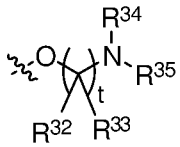
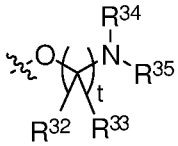
[00449] In another embodiment is a compound of Formula (IIj) wherein R^{30} is , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is F.

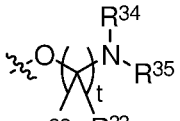
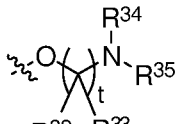


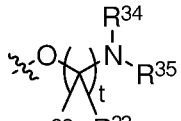
[00450] In another embodiment is a compound of Formula (IIj) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is F.

[00451] In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , and p is 0.

[00452] In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00453] In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of

Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , p is 1 and R^{31} is F.

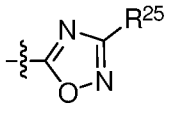
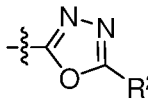
[00454] In another embodiment is a compound of Formula (IIj) wherein R^{30} is  , and p is 0.

[00455] In another embodiment is a compound of Formula (IIj) wherein n is 0. In another embodiment is a compound of Formula (IIj) wherein n is 1. In another embodiment is a compound of Formula (IIj) wherein n is 2.

[00456] In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is halogen. In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is F. In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is Cl. In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is C_1-C_6alkoxy. In another embodiment is a compound of Formula (IIj) wherein n is 1 and R^{11} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IIj) wherein n is 2 and each R^{11} is independently halogen, C_1-C_6alkyl, or C_1-C_6alkoxy.

[00457] In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IIj) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IIj) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IIj) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

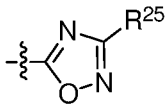
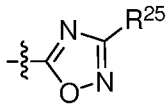
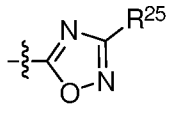
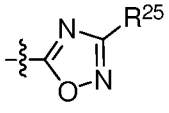
[00458] In another embodiment is a compound of Formula (IIj) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IIj) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IIj) wherein R^6 and R^7 are each hydrogen.

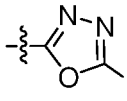
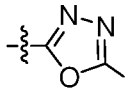
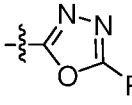
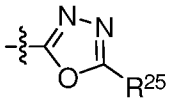
[00459] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -CN.

[00460] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00461] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are

each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00462] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is ethyl.

[00463] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^2 is  , and R^{25} is ethyl.

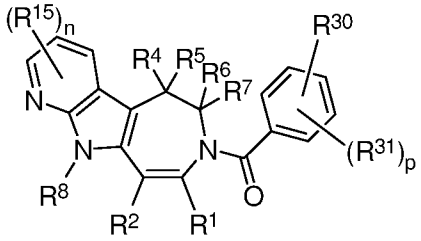
[00464] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00465] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00466] In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is selected from the group consisting of hydrogen, optionally

substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IIj) wherein R^8 is hydrogen.

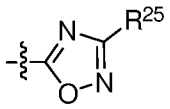
[00467] In another aspect, provided herein is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:

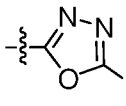


Formula (III);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26}, 

, and 

; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon

atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

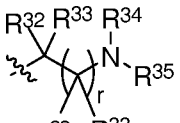
each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14}, -OC(O)OR^{12}, -OC(O)N(R^{13})R^{14}, -N(R^{13})C(O)OR^{12}, and -N(R^{13})C(O)N(R^{13})R^{14};

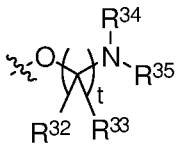
R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-



C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, ,



or ;

each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

[00468] In one embodiment is a compound of Formula (III) wherein p is 0. In another embodiment is a compound of Formula (III) wherein p is 1. In another embodiment is a compound of Formula (III) wherein p is 2. In another embodiment is a compound of Formula (III) wherein p is 3. In another embodiment is a compound of Formula (III) wherein p is 4.

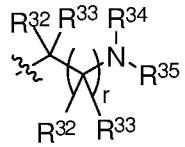
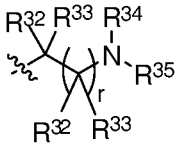
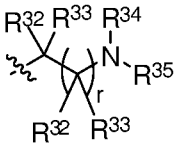
[00469] In another embodiment is a compound of Formula (III) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein p is 2 and each R^{31} is F.

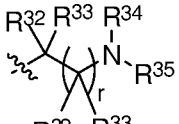
[00470] In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl,

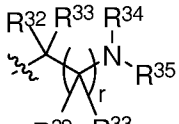
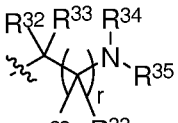
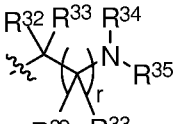
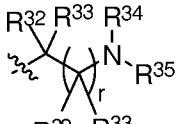
optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 2 and each R^{31} is F.

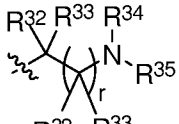
[00471] In another embodiment is a compound of Formula (III) wherein p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein p is 1 and R^{31} is F.

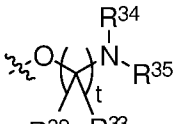
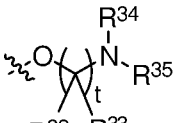
[00472] In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein R^{30} is F, p is 1 and R^{31} is F.

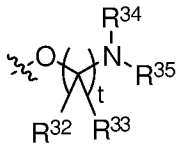
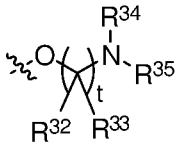
[00473] In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In

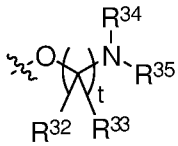
another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and each R^{31} is F.

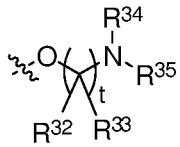
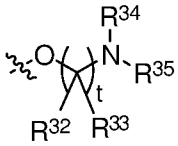
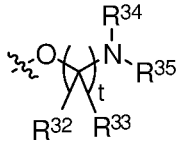
[00474] In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is F.

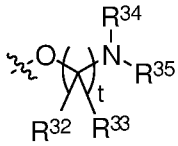
[00475] In another embodiment is a compound of Formula (III) wherein R^{30} is  , and p is 0.

[00476] In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and

each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 2 and each R^{31} is F.



[00477] In another embodiment is a compound of Formula (III) wherein R^{30} is , p is 1 and R^{31} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (III) wherein R^{30} is  , p is 1 and R^{31} is F.



[00478] In another embodiment is a compound of Formula (III) wherein R^{30} is , and p is 0.

[00479] In another embodiment is a compound of Formula (III) wherein n is 0. In another embodiment is a compound of Formula (III) wherein n is 1. In another embodiment is a compound of Formula (III) wherein n is 2. In another embodiment is a compound of Formula (III) wherein n is 3.

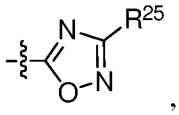
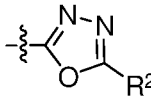
[00480] In another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is halogen. In another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is F. In

another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is Cl. In another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (III) wherein n is 1 and R^{15} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (III) wherein n is 2 and each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, $-C(O)OR^{12}$, $-C(O)N(R^{13})R^{14}$, $-OC(O)OR^{12}$, $-OC(O)N(R^{13})R^{14}$, $-N(R^{13})C(O)OR^{12}$, and $-N(R^{13})C(O)N(R^{13})R^{14}$. In another embodiment is a compound of Formula (III) wherein n is 2 and each R^{15} is independently halogen, optionally substituted C_1-C_6alkyl, or optionally substituted C_1-C_6alkoxy.

[00481] In another embodiment is a compound of Formula (III) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (III) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (III) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (III) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (III) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00482] In another embodiment is a compound of Formula (III) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (III) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (III) wherein R^6 and R^7 are each hydrogen.

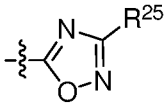
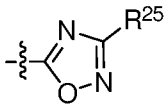
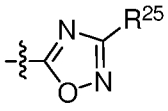
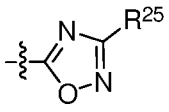
[00483] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is selected from the group consisting of -CN, $-C(O)OR^{25}$, -

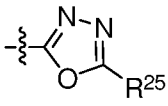
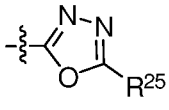
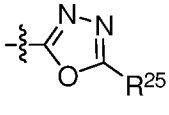
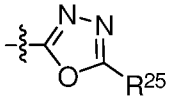
$C(O)N(R^{25})R^{26}$,  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -CN.

[00484] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)OR^{25}$, and R^{25} is ethyl.

[00485] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)N(R^{25})R^{26}$. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is $-C(O)N(R^{25})R^{26}$, and R^{25} and R^{26} are each independently optionally

substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00486] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is ethyl.

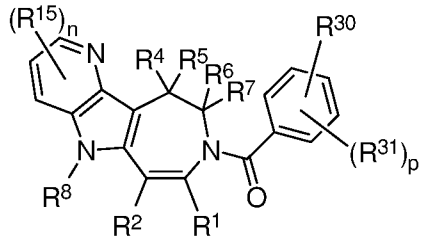
[00487] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^2 is  , and R^{25} is ethyl.

[00488] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00489] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00490] In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (III) wherein R^8 is hydrogen.

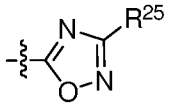
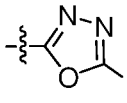
[00491] In another aspect, provided herein is a compound having the structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -

(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

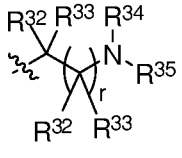
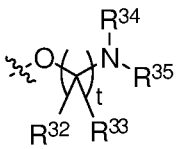
each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -$C(O)OR^{12}$, -$C(O)N(R^{13})R^{14}$, -$OC(O)OR^{12}$, -$OC(O)N(R^{13})R^{14}$, -$N(R^{13})C(O)OR^{12}$, and -$N(R^{13})C(O)N(R^{13})R^{14}$;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl,  ,  or ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

[00492] In one embodiment is a compound of Formula (IV) wherein p is 0. In another embodiment is a compound of Formula (IV) wherein p is 1. In another embodiment is a compound of Formula (IV) wherein p is 2. In another embodiment is a compound of Formula (IV) wherein p is 3. In another embodiment is a compound of Formula (IV) wherein p is 4.

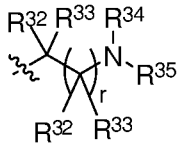
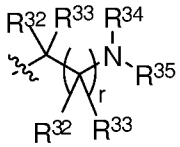
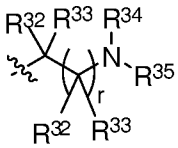
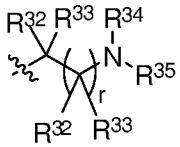
[00493] In another embodiment is a compound of Formula (IV) wherein p is 2 and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein p is 2 and each R^{31} is F.

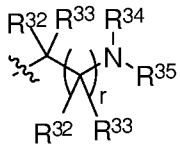
[00494] In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 2 and each R^{31} is F.

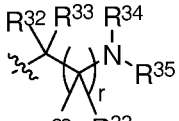
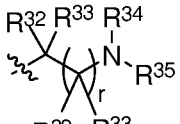
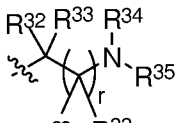
[00495] In another embodiment is a compound of Formula (IV) wherein p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein p is 1 and R^{31} is halogen, or optionally substituted C_1-

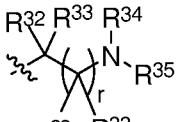
C_6alkyl. In another embodiment is a compound of Formula (IV) wherein p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein p is 1 and R^{31} is F.

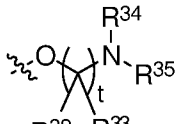
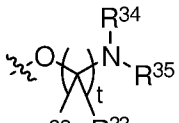
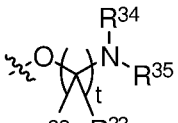
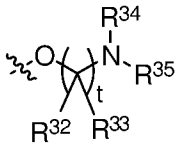
[00496] In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is F, p is 1 and R^{31} is F.

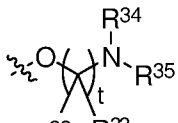
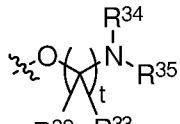
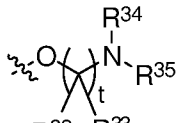
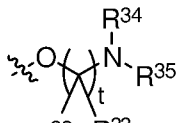
[00497] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is F.

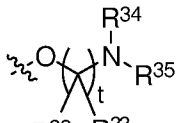
[00498] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another

embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is F.

[00499] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , and p is 0.

[00500] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2, and each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is independently halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 2 and each R^{31} is F.

[00501] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen, or optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is halogen. In another embodiment is a compound of Formula (IV) wherein R^{30} is  , p is 1 and R^{31} is F.

[00502] In another embodiment is a compound of Formula (IV) wherein R^{30} is  , and p is 0.

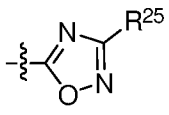
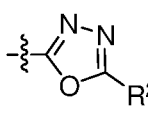
[00503] In another embodiment is a compound of Formula (IV) wherein n is 0. In another embodiment is a compound of Formula (IV) wherein n is 1. In another embodiment is a compound of Formula (IV) wherein n is 2. In another embodiment is a compound of Formula (IV) wherein n is 3.

[00504] In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is halogen. In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is F. In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is Cl. In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkoxy. In another embodiment is a compound of Formula (IV) wherein n is 1 and R^{15} is $-OCH_2CH_2OH$. In another embodiment is a compound of Formula (IV) wherein n is 2 and each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally

substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14}, -OC(O)OR^{12}, -OC(O)N(R^{13})R^{14}, -N(R^{13})C(O)OR^{12}, and -N(R^{13})C(O)N(R^{13})R^{14}. In another embodiment is a compound of Formula (IV) wherein n is 2 and each R^{15} is independently halogen, optionally substituted C_1-C_6alkyl, or optionally substituted C_1-C_6alkoxy.

[00505] In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 are each hydrogen. In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 are each methyl. In another embodiment is a compound of Formula (IV) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring. In some embodiments is a compound of Formula (IV) wherein R^4 and R^5 form an optionally substituted C_3-C_6cycloalkyl ring. In some embodiments is a compound of Formula (IV) wherein R^4 and R^5 form an optionally substituted C_2-C_7heterocycloalkyl ring.

[00506] In another embodiment is a compound of Formula (IV) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen, halogen, and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^6 and R^7 are each independently selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^6 and R^7 are each independently optionally substituted C_1-C_6alkyl. In another embodiment is a compound of Formula (IV) wherein R^6 and R^7 are each methyl. In another embodiment is a compound of Formula (IV) wherein R^6 and R^7 are each hydrogen.

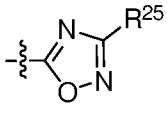
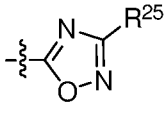
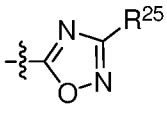
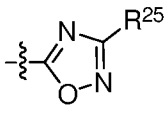
[00507] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -CN.

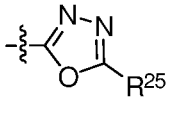
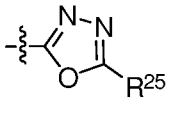
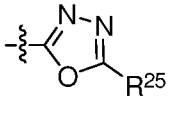
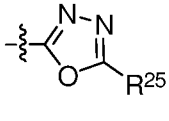
[00508] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally

substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)OR^{25}, and R^{25} is ethyl.

[00509] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are each independently unsubstituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, R^{25} is hydrogen, and R^{26} are methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are methyl. In a

further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is -C(O)N(R^{25})R^{26}, and R^{25} and R^{26} are ethyl.

[00510] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is ethyl.

[00511] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  . In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^2 is  , and R^{25} is ethyl.

[00512] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 is hydrogen. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV)

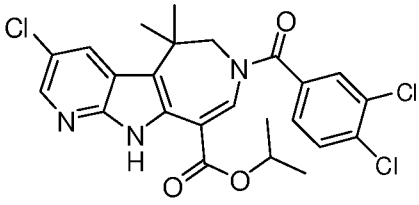
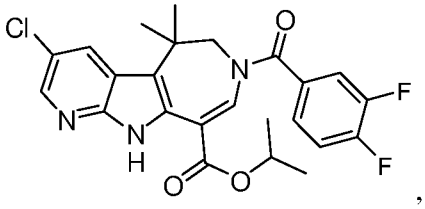
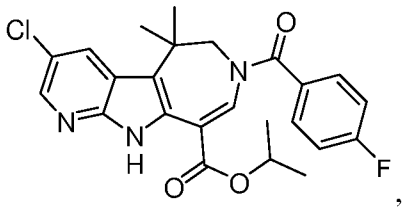
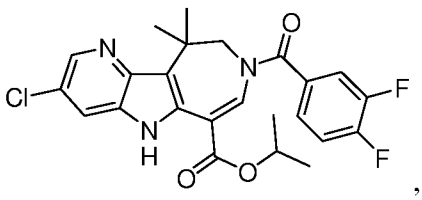
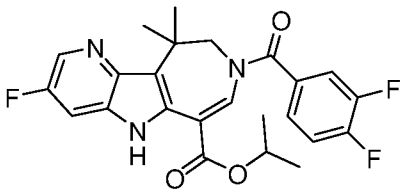
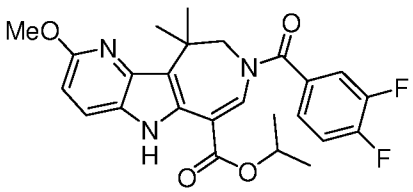
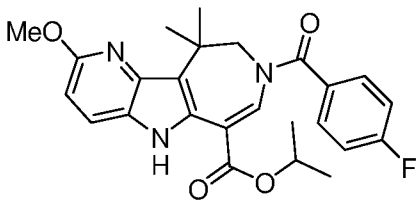
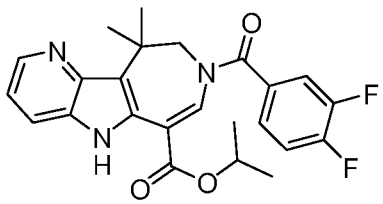
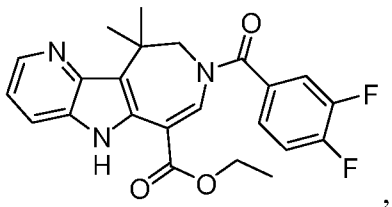
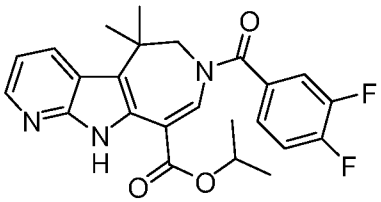
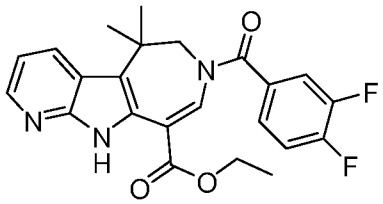
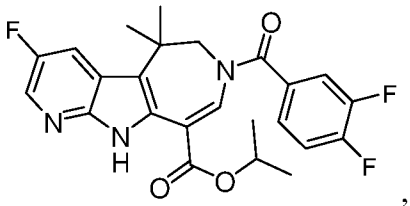
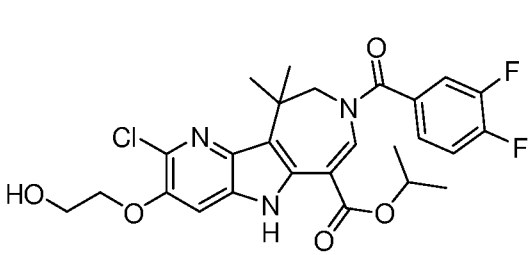
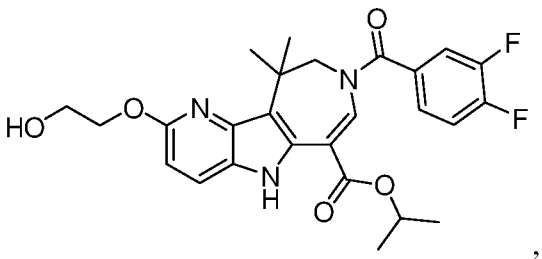
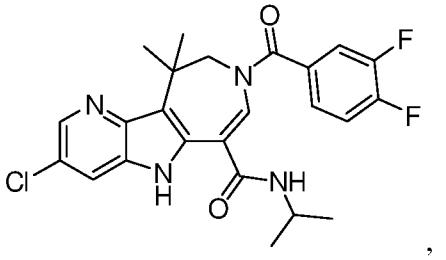
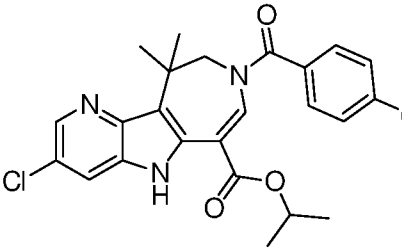
wherein R^1 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 is optionally substituted C_2-C_6alkenyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 is optionally substituted C_2-C_6alkynyl.

[00513] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted heteroaryl ring.

[00514] In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl). In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is selected from the group consisting of hydrogen, and optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is optionally substituted C_1-C_6alkyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is methyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is ethyl. In a further embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^8 is hydrogen.

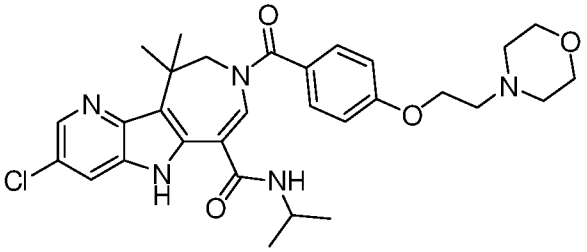
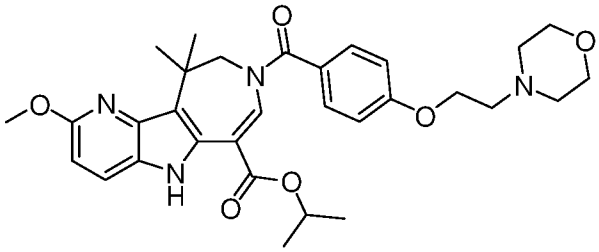
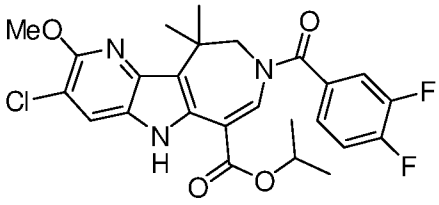
[00515] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[00516] In some embodiments is a compound selected from:

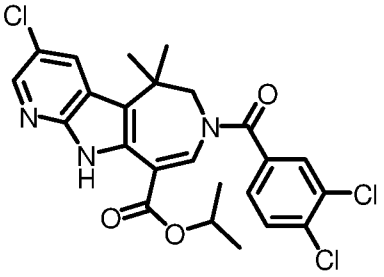
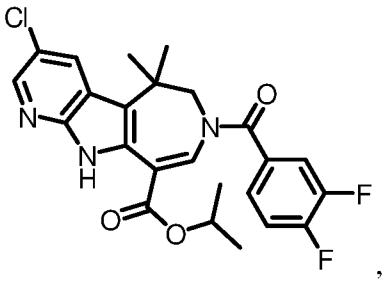
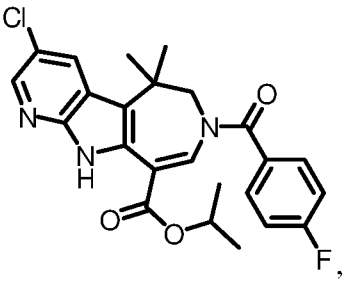
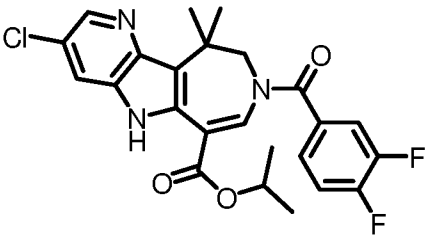
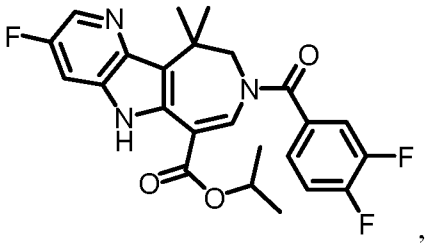
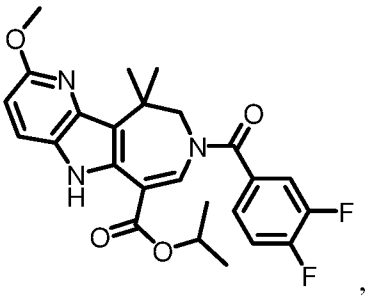

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

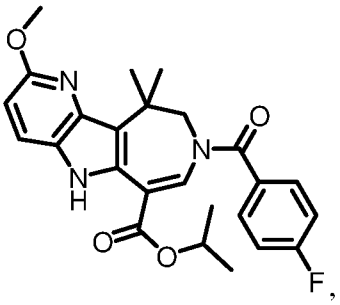
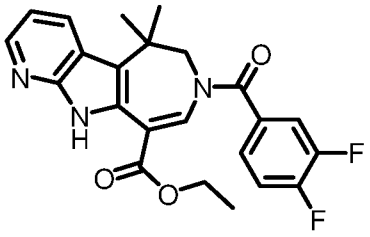
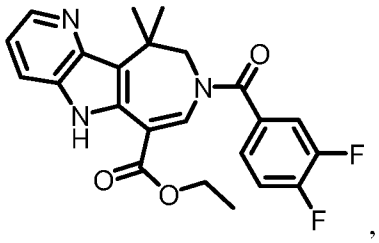
,

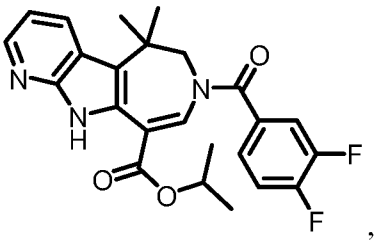
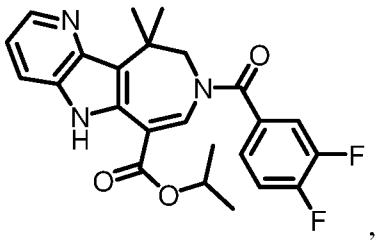
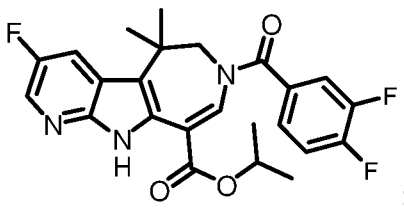
,


,

,

or ; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

[00517] In some embodiments is a compound selected from:

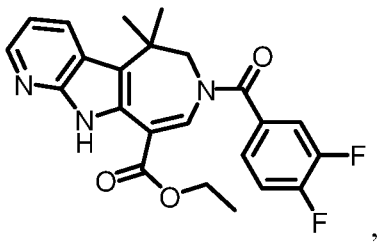
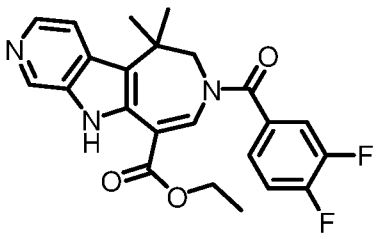
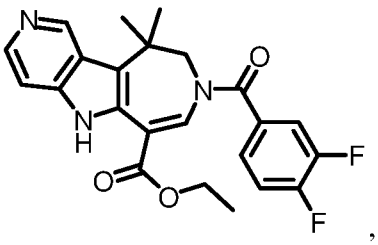

,

,

,

,

,

,

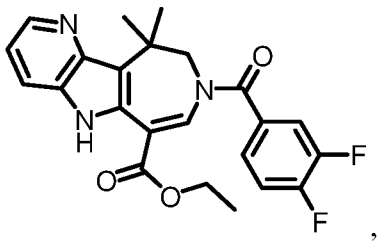
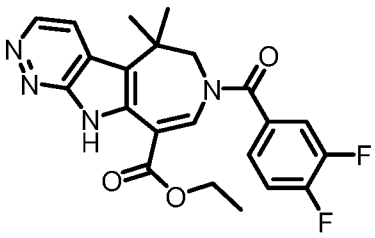
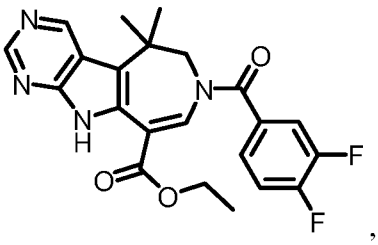
 ,  ,  ,

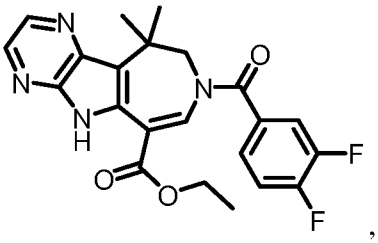
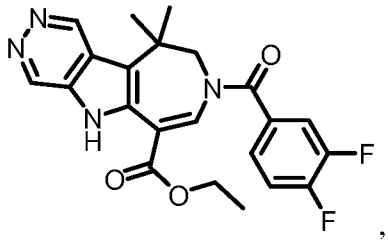
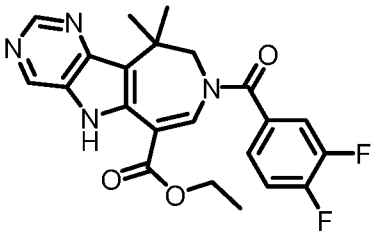
 ,  , and  ;

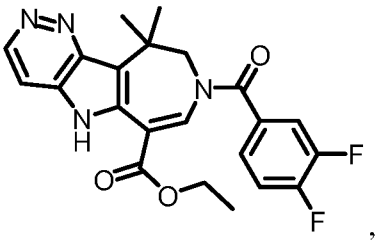
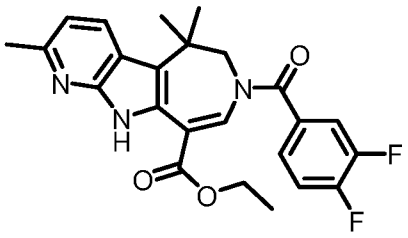
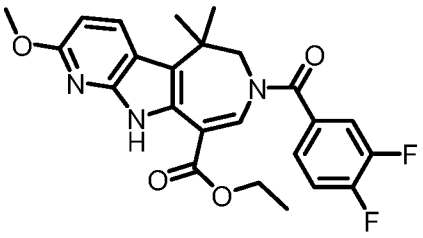
or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

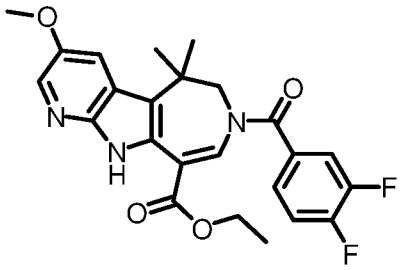
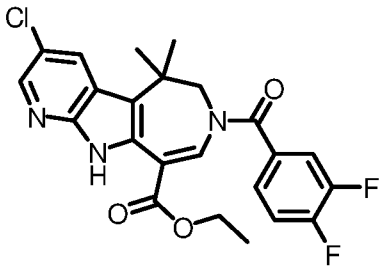
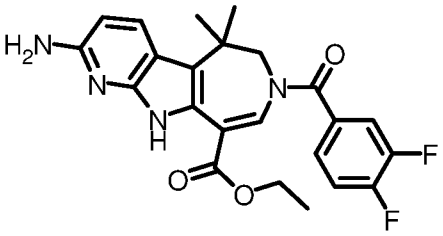
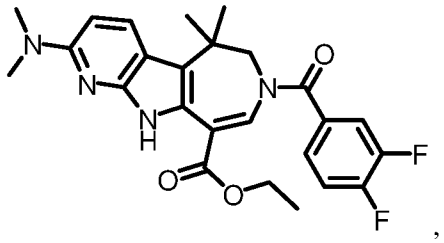
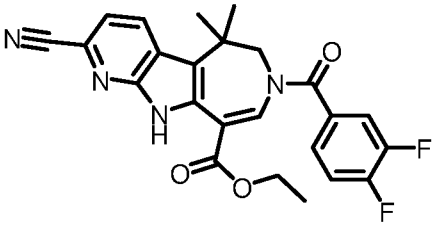
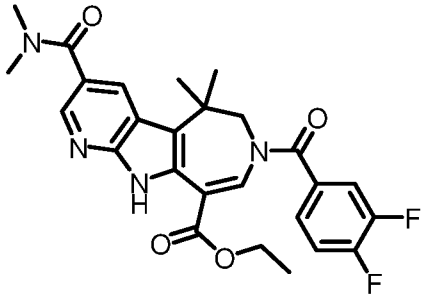
[00518] In some embodiments is a compound selected from:

 ,  ,  ,

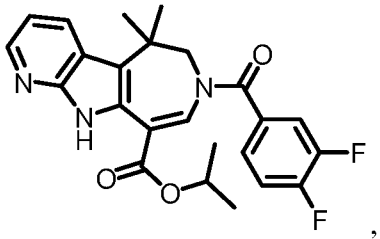
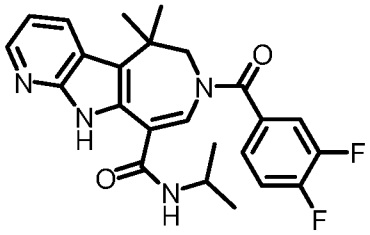
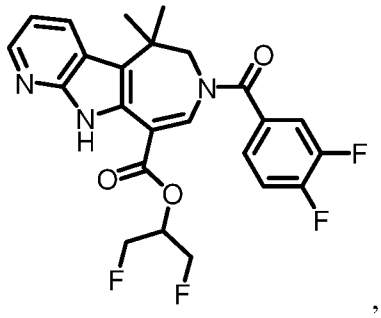
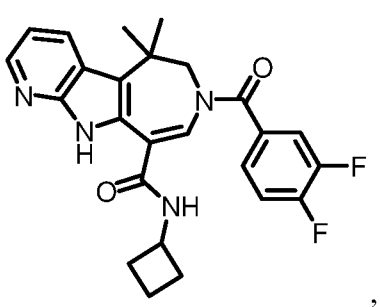
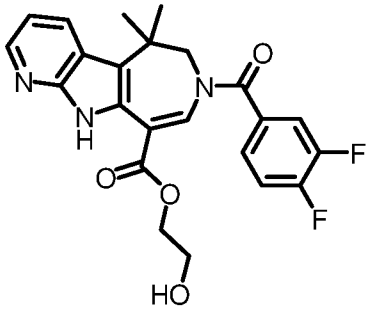
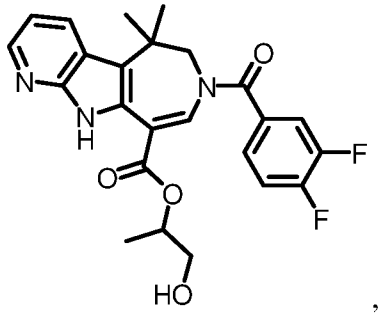
 ,  ,  ,

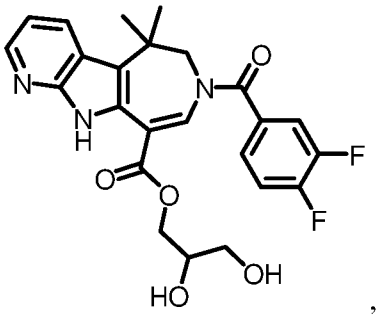
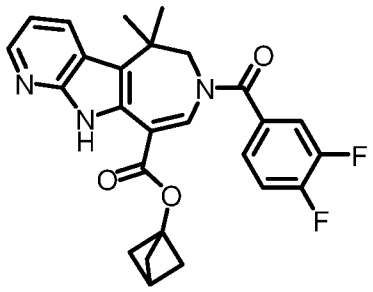
 ,  ,  ,

 ,  ,  ,

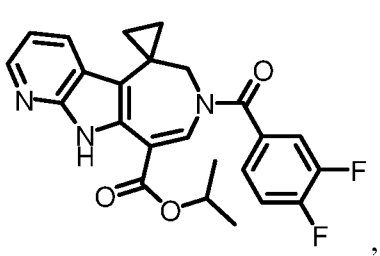
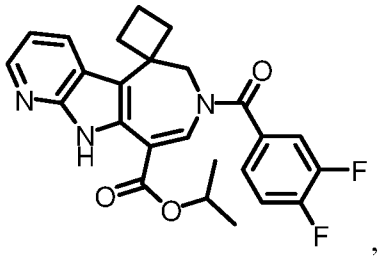
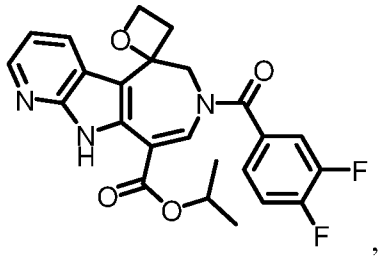
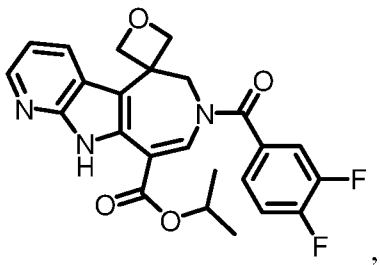
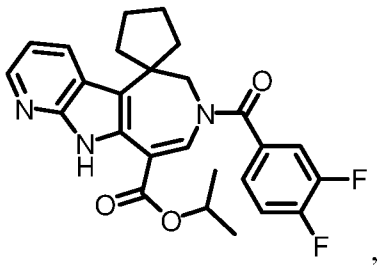
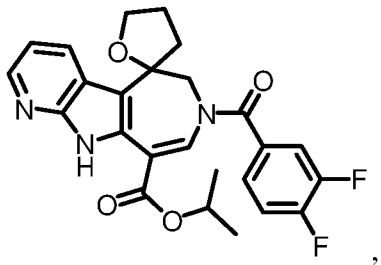
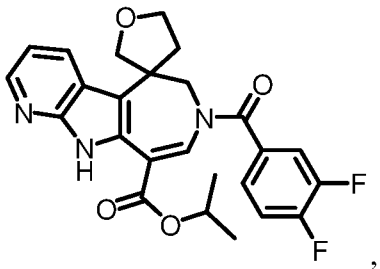
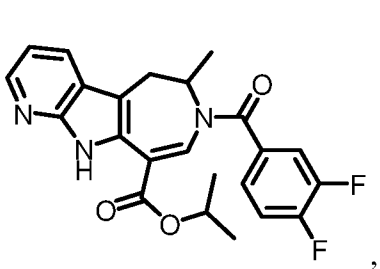
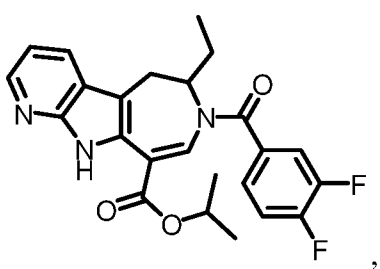
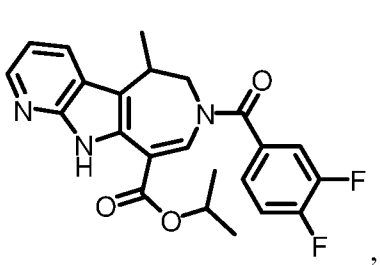
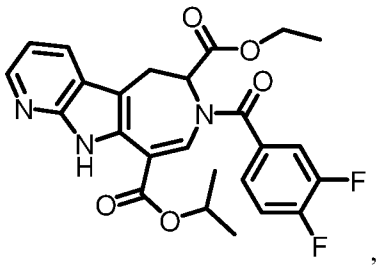
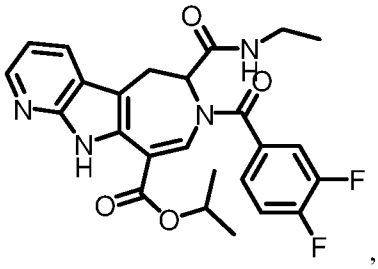
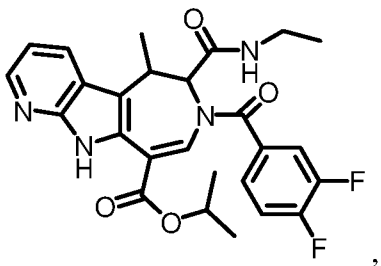
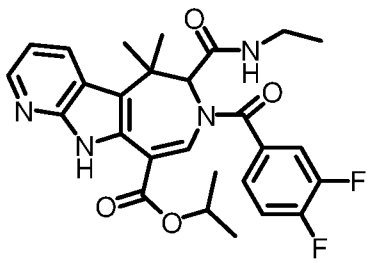
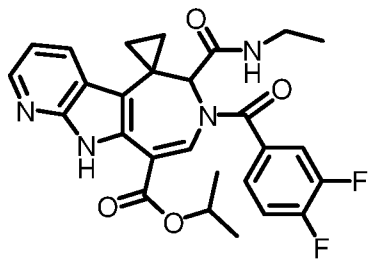

,

,

,

,

, and

; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

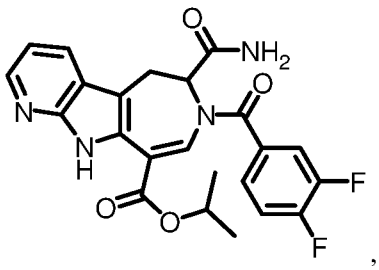
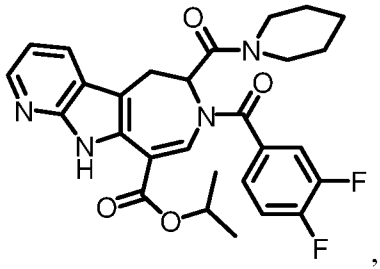
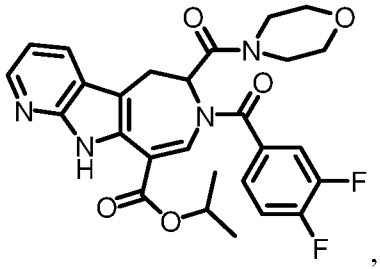
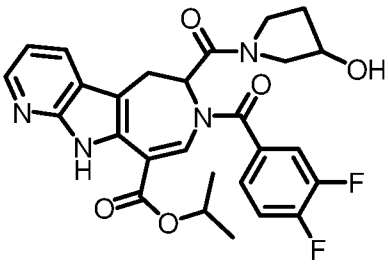
[00519] In some embodiments is a compound selected from:


,

,

,

,

,

,


, and 
; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

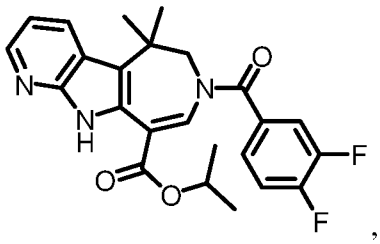
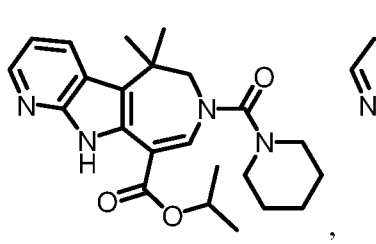
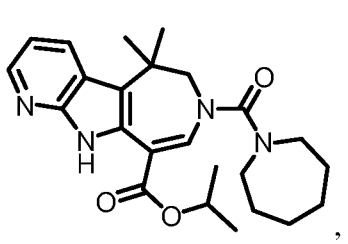
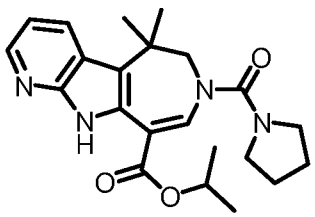
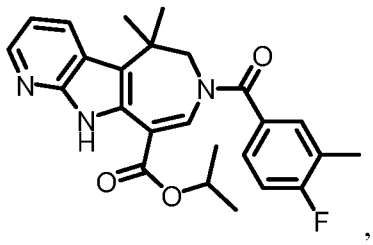
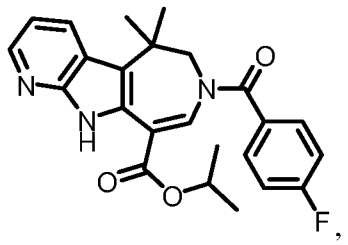
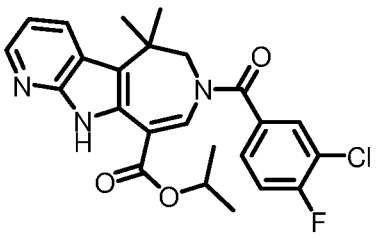
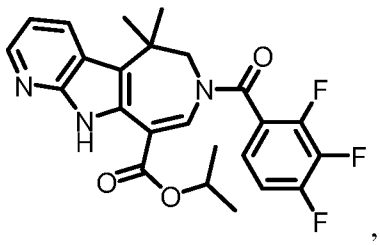
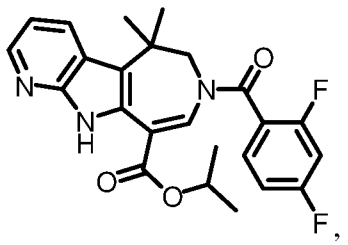
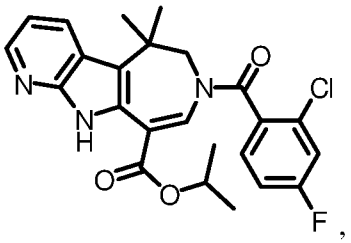
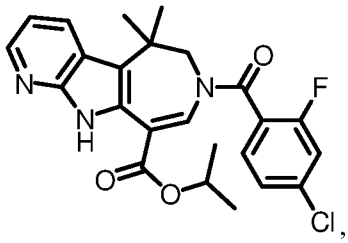
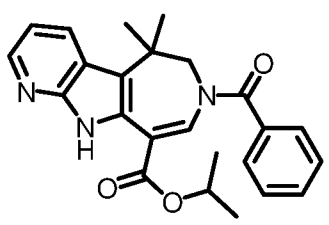
[00520] In some embodiments is a compound selected from:

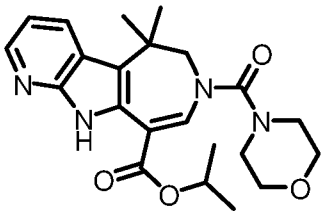
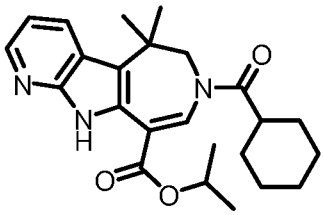
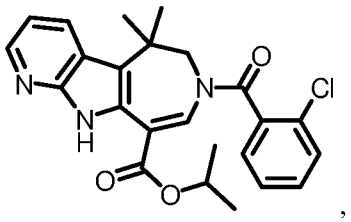
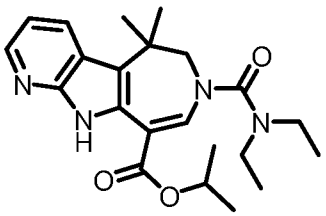
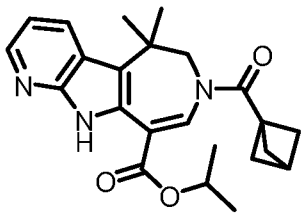

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

and ; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

[00521] In some embodiments is a compound selected from:


,

,

,

, and

; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

[00522] In some embodiments, the therapeutic agent(s) (e.g. compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV)) is present in the pharmaceutical composition as a pharmaceutically acceptable salt. In some embodiments, any compound described above is suitable for any method or composition described herein.

[00523] In certain embodiments, the compounds presented herein possess one or more stereocenters and each center independently exists in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. In some embodiments, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) is used as a single enantiomer. In some embodiments, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) is used as a racemic mixture.

[00524] The methods and formulations described herein include the use of *N*-oxides (if appropriate), crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structures presented herein, as well as active metabolites of these compounds having the same type of activity.

[00525] In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

[00526] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug

may also have improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00527] Prodrugs of the compounds described herein include, but are not limited to, esters, ethers, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, and sulfonate esters. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference. In some embodiments, a hydroxyl group in the compounds disclosed herein is used to form a prodrug, wherein the hydroxyl group is incorporated into an acyloxyalkyl ester, alkoxycarbonyloxyalkyl ester, alkyl ester, aryl ester, phosphate ester, sugar ester, ether, and the like.

[00528] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00529] In specific embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In other embodiments, the compounds described herein exist in unsolvated form.

[00530] In some embodiments, the compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) described herein include solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

[00531] In some embodiments, sites on the compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV)

disclosed herein are susceptible to various metabolic reactions. Therefore incorporation of appropriate substituents at the places of metabolic reactions will reduce, minimize or eliminate the metabolic pathways. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium or an alkyl group.

[00532] In some embodiments, the compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) disclosed herein are isotopically-labeled, which are identical to those recited in the various formulae and structures presented 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. In some embodiments, one or more hydrogen atoms are replaced with deuterium. In some embodiments, metabolic sites on the compounds described herein are deuterated. In some embodiments, substitution with deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00533] In some embodiments, compounds described herein, such as compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), are in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds described herein include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, melting points, density, hardness, crystal shape, optical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[00534] The screening and characterization of the pharmaceutically acceptable salts, polymorphs and/or solvates may be accomplished using a variety of techniques including, but not limited to, thermal analysis, x-ray diffraction, spectroscopy, vapor sorption, and microscopy. Thermal analysis methods address thermo chemical degradation or thermo physical processes including, but not limited to, polymorphic transitions, and such methods are used to analyze the relationships between polymorphic forms, determine weight loss, to find the glass transition temperature, or for excipient compatibility studies. Such methods include, but are not limited to, Differential scanning calorimetry (DSC), Modulated Differential Scanning Calorimetry (MDCS), Thermogravimetric analysis (TGA), and Thermogravi-metric and Infrared analysis (TG/IR). X-ray diffraction methods include, but are not limited to, single crystal and powder diffractometers and synchrotron sources. The various spectroscopic techniques used include, but

are not limited to, Raman, FTIR, UV-VIS, and NMR (liquid and solid state). The various microscopy techniques include, but are not limited to, polarized light microscopy, Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (EDX), Environmental Scanning Electron Microscopy with EDX (in gas or water vapor atmosphere), IR microscopy, and Raman microscopy.

[00535] Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

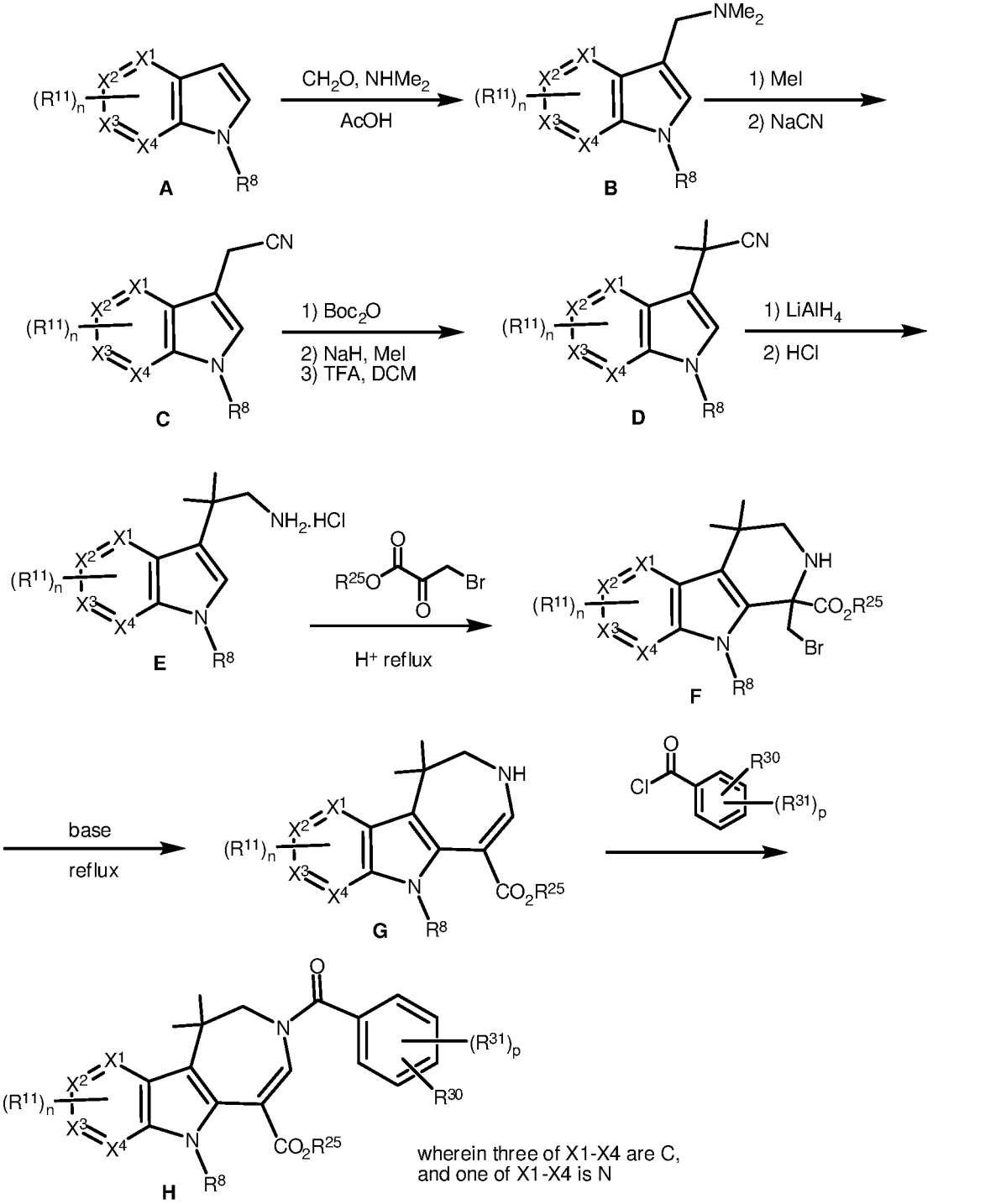
Synthesis of Compounds

[00536] In some embodiments, the synthesis of compounds described herein are accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof. In addition, solvents, temperatures and other reaction conditions presented herein may vary.

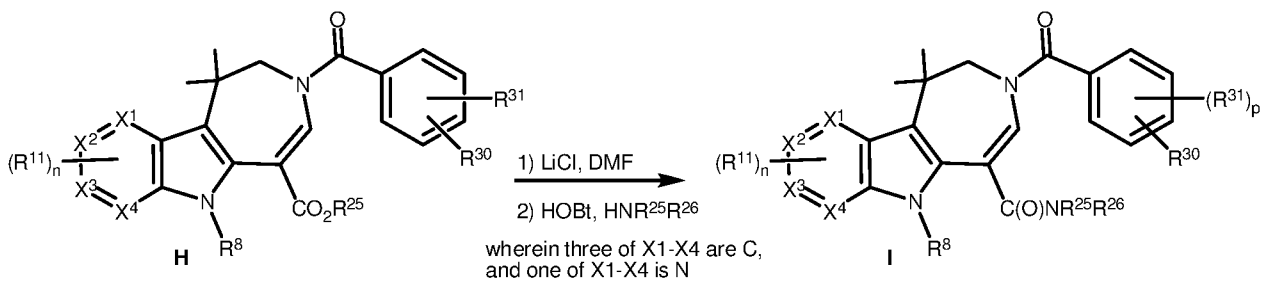
[00537] In other embodiments, the starting materials and reagents used for the synthesis of the compounds described herein are synthesized or are obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, FischerScientific (Fischer Chemicals), and AcrosOrganics. In further embodiments, the compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein as well as those that are recognized in the field, such as described, for example, in Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, Advanced Organic Chemistry 4th Ed., (Wiley 1992); Carey and Sundberg, Advanced Organic Chemistry 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, Protective Groups in Organic Synthesis 3rd Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as disclosed herein may be derived from reactions and the reactions may be modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formulae as provided herein.

[00538] In some embodiments, the compounds described herein are prepared as outlined in the following schemes.

Scheme 1



Scheme 2



Use of Protecting Groups

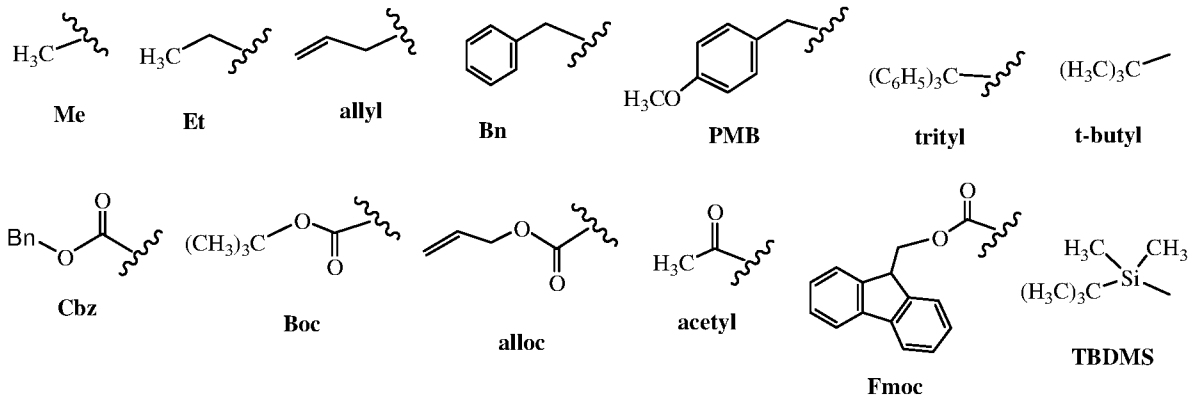
[00539] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, in order to avoid their unwanted participation in reactions. Protecting groups are used to block some or all of the reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal.

[00540] Protective groups can be removed by acid, base, reducing conditions (such as, for example, hydrogenolysis), and/or oxidative conditions. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[00541] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, which include conversion to alkyl esters, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[00542] Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd^0-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00543] Typically blocking/protecting groups may be selected from:



[00544] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure).

Certain Terminology

[00545] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by reference. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[00546] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[00547] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00548] Definition of standard chemistry terms may be found in reference works, including but not limited to, Carey and Sundberg "Advanced Organic Chemistry 4th Ed." Vols. A (2000) and

B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology.

[00549] Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those recognized in the field. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[00550] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

[00551] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. C_1-C_x refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

[00552] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl groups may or may not include units of unsaturation. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any units of unsaturation (i.e. a carbon-carbon double bond or a carbon-carbon triple bond). The alkyl group may also be an "unsaturated alkyl" moiety, which means that it contains at least one unit of unsaturation. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[00553] The "alkyl" group may have 1 to 6 carbon atoms (whenever it appears herein, a numerical range such as "1 to 6" refers to each integer in the given range; *e.g.*, "1 to 6 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C_1-C_6 alkyl" or similar designations. By way of example only, "C_1-C_6 alkyl" indicates that there are one to six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, n-propyl, iso-

propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, neo-pentyl, hexyl, propen-3-yl (allyl), cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl. Alkyl groups can be substituted or unsubstituted. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group).

[00554] An "alkoxy" refers to a "-O-alkyl" group, where alkyl is as defined herein.

[00555] The term "alkenyl" refers to a type of alkyl group in which two atoms of the alkyl group form a double bond that is not part of an aromatic group. Non-limiting examples of an alkenyl group include $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $-CH=C(CH_3)_2$ and $-C(CH_3)=CHCH_3$. The alkenyl moiety may be branched, straight chain, or cyclic (in which case, it would also be known as a "cycloalkenyl" group). Alkenyl groups may have 2 to 6 carbons. Alkenyl groups can be substituted or unsubstituted. Depending on the structure, an alkenyl group can be a monoradical or a diradical (i.e., an alkenylene group).

[00556] The term "alkynyl" refers to a type of alkyl group in which the two atoms of the alkyl group form a triple bond. Non-limiting examples of an alkynyl group include $-C\equiv CH$, $-C\equiv CCH_3$, $-C\equiv CCH_2CH_3$ and $-C\equiv CCH_2CH_2CH_3$. The "R" portion of the alkynyl moiety may be branched, straight chain, or cyclic. An alkynyl group can have 2 to 6 carbons. Alkynyl groups can be substituted or unsubstituted. Depending on the structure, an alkynyl group can be a monoradical or a diradical (i.e., an alkynylene group).

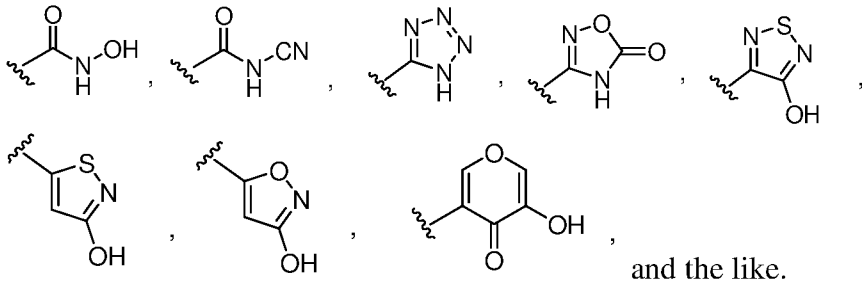
[00557] "Amino" refers to a $-NH_2$ group.

[00558] The term "alkylamine" or "alkylamino" refers to the $-N(alkyl)_xH_y$ group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, can optionally form a cyclic ring system. "Dialkylamino" refers to a $-N(alkyl)_2$ group, where alkyl is as defined herein.

[00559] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term "aromatic" includes both aryl groups (*e.g.*, phenyl, naphthalenyl) and heteroaryl groups (*e.g.*, pyridinyl, quinolinyl).

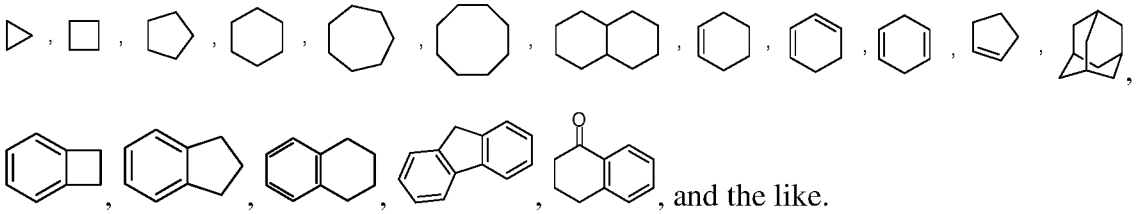
[00560] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

[00561] "Carboxy" refers to $-CO_2H$. In some embodiments, carboxy moieties may be replaced with a "carboxylic acid bioisostere", which refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisosteres of a carboxylic acid include, but are not limited to,



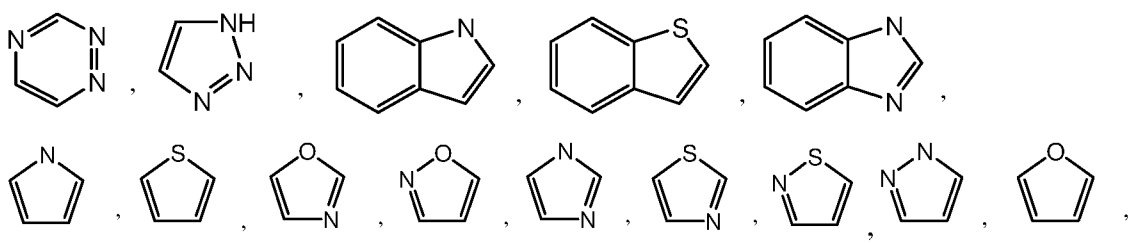
and the like.

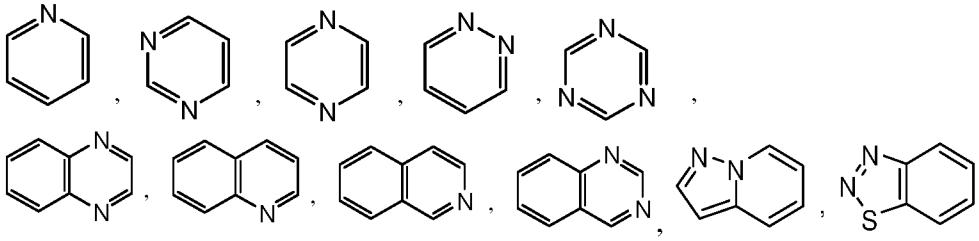
[00562] The term "cycloalkyl" refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



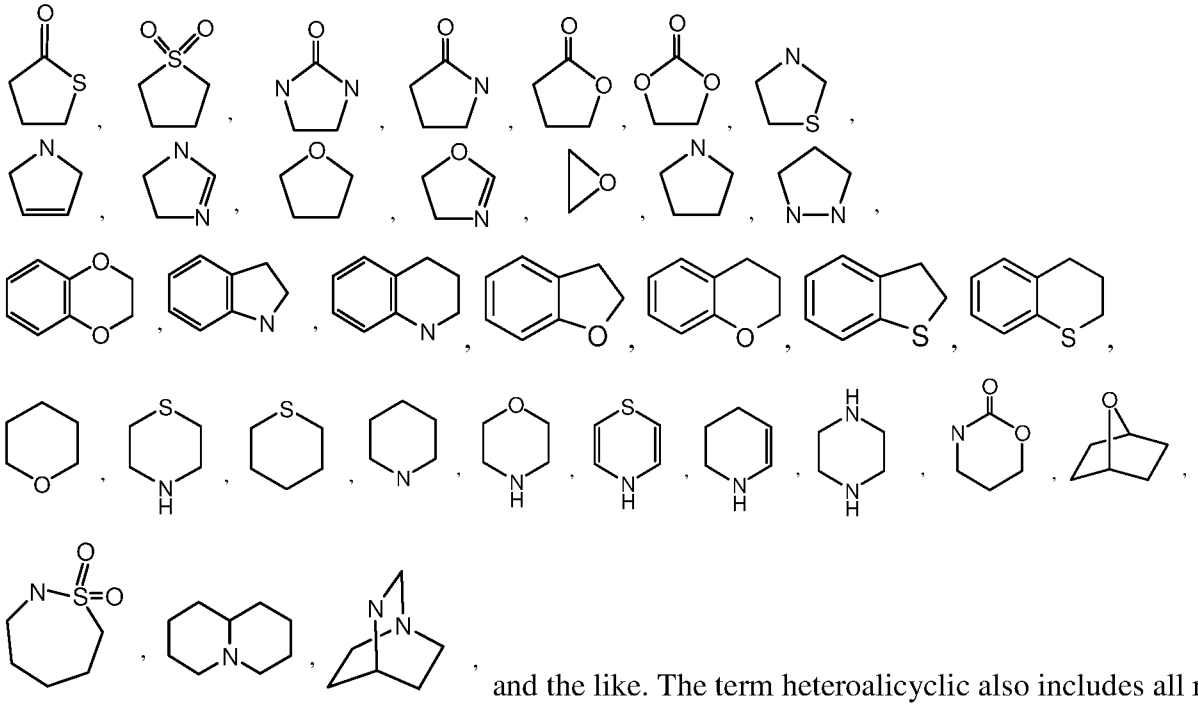
and the like.

[00563] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. Polycyclic heteroaryl groups may be fused or non-fused. Illustrative examples of heteroaryl groups include the following moieties:




and the like.

[00564] A "heterocycloalkyl" group or "heteroalicyclic" group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:


and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring).

[00565] The term "halo" or, alternatively, "halogen" means fluoro, chloro, bromo and iodo.

[00566] The term "haloalkyl" refers to an alkyl group that is substituted with one or more halogens. The halogens may the same or they may be different. Non-limiting examples of haloalkyls include $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF(CH_3)_3$, and the like.

[00567] The terms "fluoroalkyl" and "fluoroalkoxy" include alkyl and alkoxy groups, respectively, that are substituted with one or more fluorine atoms. Non-limiting examples of fluoroalkyls include $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CF(CH_3)_3$, and the

like. Non-limiting examples of fluoroalkoxy groups, include -OCF_3, -$OCHF_2$, -OCH_2F, -OCH_2CF_3, -OCF_2CF_3, -$OCF_2CF_2CF_3$, -$OCF(CH_3)_2$, and the like.

[00568] The term "heteroalkyl" refers to an alkyl radical where one or more skeletal chain atoms is selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, -CH_2-O-CH_3, -CH_2-CH_2-O-CH_3, -CH_2-NH-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-N(CH_3)-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2-CH_3, -CH_2-CH_2,-S(O)-CH_3, -CH_2-CH_2-S($O)_2$-CH_3, -CH_2-NH-OCH_3, –CH_2-O-Si($CH_3)_3$, -CH_2-CH=N-OCH_3, and -CH=CH-N(CH_3)-CH_3. In addition, up to two heteroatoms may be consecutive, such as, by way of example, -CH_2-NH-OCH_3 and –CH_2-O-Si($CH_3)_3$. Excluding the number of heteroatoms, a "heteroalkyl" may have from 1 to 6 carbon atoms.

[00569] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[00570] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00571] As used herein, the substituent "R" appearing by itself and without a number designation refers to a substituent selected from among from alkyl, haloalkyl, heteroalkyl, alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon), and heterocycloalkyl.

[00572] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, -OH, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, -CN, alkyne, C_1-C_6alkylalkyne, halo, acyl, acyloxy, -CO_2H, -CO_2-alkyl, nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups (e.g. –NH_2, -NHR, -N($R)_2$), and the protected derivatives thereof. In some embodiments, optional substituents are independently selected from halogen, -CN, -NH_2, -NH(CH_3), -N($CH_3)_2$, -OH, -CO_2H, -CO_2alkyl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)N(alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(alkyl)$_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are independently selected from halogen, -CN, -NH_2, -OH, -NH(CH_3), -N($CH_3)_2$, -CH_3, -CH_2CH_3, -CF_3, -OCH_3, and -OCF_3. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some

embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic, saturated or unsaturated carbon atoms, excluding aromatic carbon atoms) includes oxo (=O).

[00573] The methods and formulations described herein include the use of crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds having the structure of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), as well as active metabolites of these compounds having the same type of activity.

[00574] As used herein, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

[00575] The term a "therapeutically effective amount" as used herein refers to the amount of an FXR modulator that, when administered to a mammal in need, is effective to at least partially ameliorate or to at least partially prevent diseases, disorders or conditions described herein.

[00576] As used herein, the term "expression" includes the process by which polynucleotides are transcribed into mRNA and translated into peptides, polypeptides, or proteins.

[00577] The term "activator" is used in this specification to denote any molecular species that results in activation of the indicated receptor, regardless of whether the species itself binds to the receptor or a metabolite of the species binds to the receptor when the species is administered topically. Thus, the activator can be a ligand of the receptor or it can be an activator that is metabolized to the ligand of the receptor, i.e., a metabolite that is formed in tissue and is the actual ligand.

[00578] The term "antagonist" as used herein, refers to a small -molecule agent that binds to a nuclear hormone receptor and subsequently decreases the agonist induced transcriptional activity of the nuclear hormone receptor.

[00579] The term "agonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently increases nuclear hormone receptor transcriptional activity in the absence of a known agonist.

[00580] The term "inverse agonist" as used herein, refers to a small-molecule agent that binds to a nuclear hormone receptor and subsequently decreases the basal level of nuclear hormone receptor transcriptional activity that is present in the absence of a known agonist.

[00581] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00582] The term "FXR modulator" includes FXR agonists, antagonists and tissue selective FXR modulators, as well as other agents that induce the expression and/or protein levels of FXR in cells.

[00583] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human. Those skilled in the art recognize that a therapy which reduces the severity of a pathology in one species of mammal is predictive of the effect of the therapy on another species of mammal.

[00584] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Routes of Administration

[00585] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00586] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical compositions and methods of administration of FXR modulators

[00587] Administration of FXR modulators as described herein can be in any pharmacological form including a therapeutically effective amount of an FXR modulator alone or in combination with a pharmaceutically acceptable carrier.

[00588] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Additional details about suitable excipients for pharmaceutical compositions described herein may be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00589] A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) described herein, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) can be used singly or in combination with one or more therapeutic agents as components of mixtures (as in combination therapy).

[00590] The pharmaceutical formulations described herein can be administered to a subject by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. Moreover, the pharmaceutical compositions described herein, which include a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) described herein, can be formulated into any suitable

dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00591] Pharmaceutical compositions including a compound described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00592] Dose administration can be repeated depending upon the pharmacokinetic parameters of the dosage formulation and the route of administration used.

[00593] It is especially advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on (a) the unique characteristics of the FXR modulator and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. The specific dose can be readily calculated by one of ordinary skill in the art, e.g., according to the approximate body weight or body surface area of the patient or the volume of body space to be occupied. The dose will also be calculated dependent upon the particular route of administration selected. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those of ordinary skill in the art. Such calculations can be made without undue experimentation by one skilled in the art in light of the FXR modulator activities disclosed herein in assay preparations of target cells. Exact dosages are determined in conjunction with standard dose-response studies. It will be understood that the amount of the composition actually administered will be determined by a practitioner, in the light of the relevant circumstances including the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration.

[00594] Toxicity and therapeutic efficacy of such FXR modulators can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, for example, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic

effects is the therapeutic index and it can be expressed as the ratio LD_{50} /ED_{50}. FXR modulators that exhibit large therapeutic indices are preferred. While FXR modulators that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such modulators to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[00595] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such FXR modulators lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any FXR modulator used in a method described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of FXR modulator that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

Methods of Dosing and Treatment Regimens

[00596] The compounds described herein can be used in the preparation of medicaments for the modulation of FXR, or for the treatment of diseases or conditions that would benefit, at least in part, from modulation of FXR. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate or hydrate thereof, in therapeutically effective amounts to said subject.

[00597] The compositions containing the compound(s) described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. Amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician.

[00598] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like.

When used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00599] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00600] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday can vary between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00601] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00602] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease or condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be determined in a manner recognized in the field according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of about 0.01 mg per day to about 5000 mg per day, in some embodiments, about 1 mg per day to about 1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00603] The pharmaceutical composition described herein may 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 compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

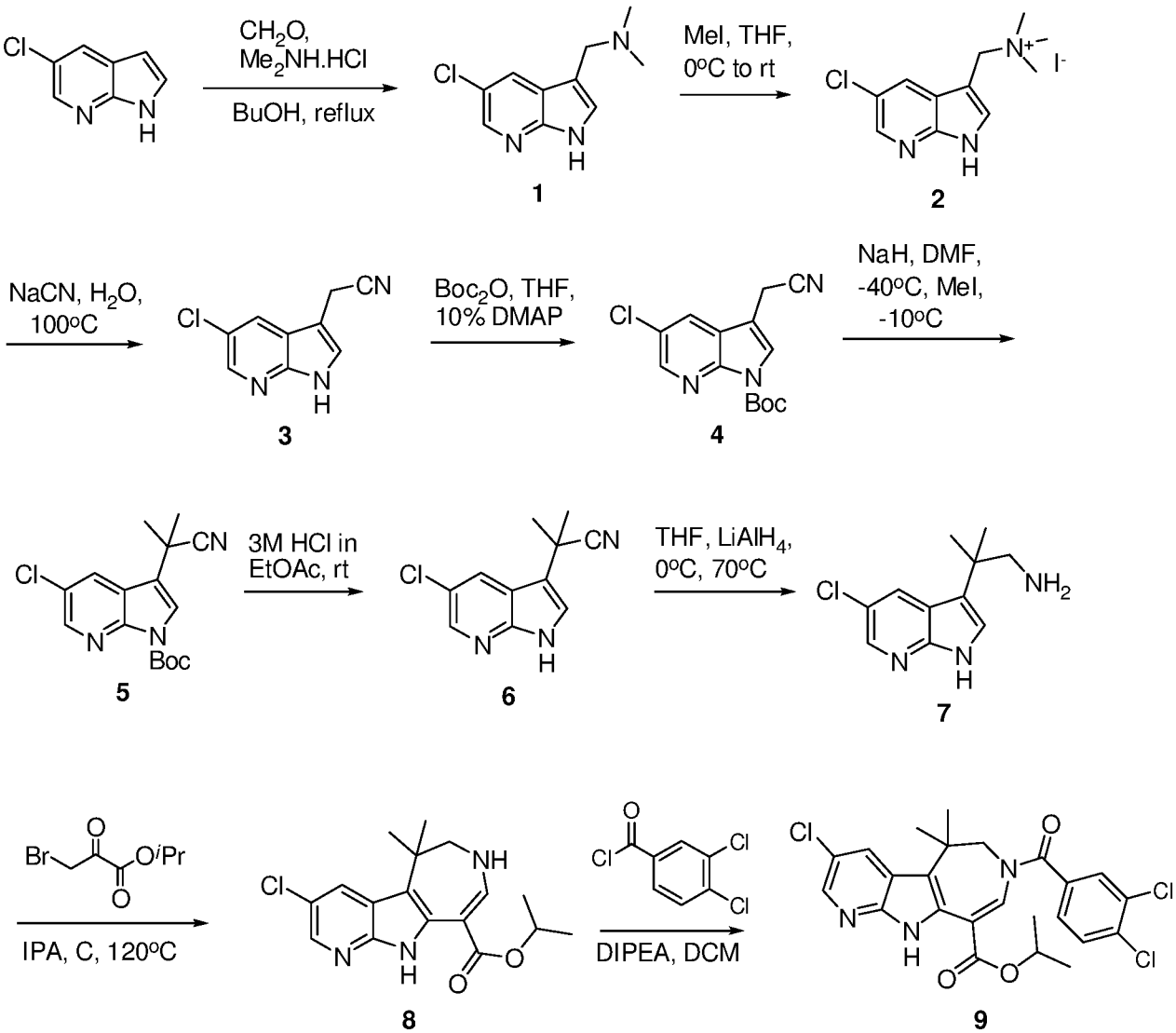
[00604] The daily dosages appropriate for the compounds described herein described herein are from about 0.001 mg/kg to about 30 mg/kg. In one embodiment, the daily dosages are from about 0.01 mg/kg to about 10 mg/kg. An indicated daily dosage in the larger mammal, including, but not limited to, humans, is in the range from about 0.1 mg to about 1000 mg, conveniently administered in a single dose or in divided doses, including, but not limited to, up to four times a day or in extended release form. Suitable unit dosage forms for oral administration include from about 1 to about 500 mg active ingredient. In one embodiment, the unit dosage is about 1 mg, about 5 mg, about, 10 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 400 mg, or about 500 mg. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00605] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

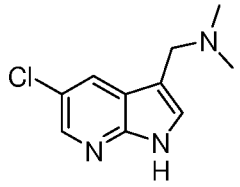
EXAMPLES

[00606] The following examples are offered for purposes of illustration, and are not intended to limit the scope of the claims provided herein. All literature citations in these examples and throughout this specification are incorporated herein by references for all legal purposes to be served thereby. The starting materials and reagents used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Acros Organics, Fluka, and Fischer Scientific.

Example 1: Synthesis of propan-2-yl 4-chloro-12-(3,4-dichlorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (8)



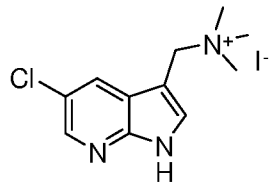
Step 1: 1-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,N-dimethylmethanamine (1)



1

[00607] Paraformaldehyde (2.2 g, 72 mmol) and dimethylamine hydrochloride (5.9 g, 72 mmol) were added to a stirred solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (10 g, 65.6 mmol) in *n*-butanol (60 mL). The reaction was heated at reflux for 3 h. The solution was allowed to cool to rt and quenched by addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (500 mLx3). The organic extracts were combined, washed with brine (500 mL), dried over anhydrous sodium sulfate, and concentrated to give compound **1** (13.8 g, 100% yield), which was used in the next reaction without purification. LC-MS: 210.21 (M+H), $C_{10}H_{12}ClN_3$. ^1H NMR (DMSO, 400 MHz) δ 12.33 (br, 1H), 10.727 (br, 1H), 8.48 (s, 1H), 8.27 (s, 1H), 7.85 (s, 1H), 4.41 (s, 2H), 2.69 (s, 6H).

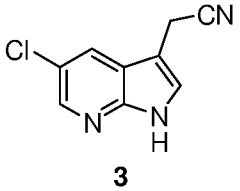
Step 2: 1-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-N,N,N-trimethylmethanaminium iodide (2)



2

[00608] Iodomethane (10 mL, 164 mmol) was added dropwise to a stirred solution of compound **1** (13.8 g, 65.6 mmol) in THF (300 mL) at 0°C. The reaction was then stirred at rt overnight. The resulting precipitate was collected and dried to give compound **2** (21 g, 91% yield), which was used in the next reaction without purification. LC-MS: 224.22 (M+), $C_{11}H_{15}ClIN_3$. ^1H NMR (DMSO, 400 MHz) δ: 12.47 (br, 1H), 8.51-8.46 (m, 1H), 8.32 (s, 1H), 7.98-7.94 (m, 1H), 4.69 (s, 2H), 3.13(s, 3H), 3.06 (s, 6H).

Step 3: 2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)acetonitrile (3)

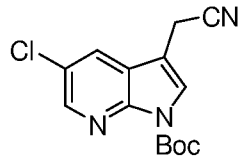


3

[00609] Sodium cyanide (6 g, 120 mmol) was added to a stirred solution of compound **2** (21g, 60 mmol) in water (750 mL). The reaction was stirred for 2 h at 100°C then cooled. The mixture was extracted with ethyl acetate (200 mLx3). The organic extracts were combined, dried over

anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography (DCM/MeOH, 50/1) give compound **3** (6.5 g, 52% yield) as a white solid. LC-MS: 190.07 (M-H), $C_9H_6ClN_3$. ^1H NMR (DMSO, 400 MHz) δ: 11.98 (br, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 7.59 (s, 1H), 4.06 (s, 2H).

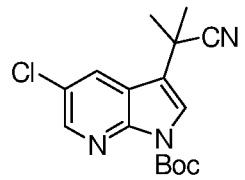
Step 4: *tert*-Butyl 5-chloro-3-(cyanomethyl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (4)



4

[00610] Boc_2O (7 g, 32.3 mmol) was added to a stirred solution of compound **3** (6.5 g, 34 mmol) and DMAP (410 mg, 3.4 mmol) in THF (170 mL). The reaction was stirred for 10 min at rt. The reaction was quenched by addition of citric acid (10%). The resulting mixture was extracted with ethyl acetate. The organics were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give compound **4** (6 g, 60% yield) as white solid. LC-MS: 292.3 (M+H), $C_{14}H_{14}ClN_3O_2$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 8.51 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 3.78 (s, 2H), 1.69 (s, 9H).

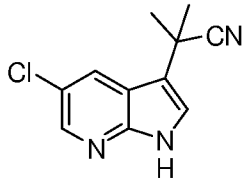
Step 5: *tert*-Butyl 5-chloro-3-(2-cyanopropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (5)



5

[00611] A suspension of sodium hydride (1.37 g, 34.2 mmol, 60% in mineral oil) in DMF (40 mL) was cooled to -40°C under nitrogen. A mixture of compound **4** (4.0 g, 13.7 mmol) and iodomethane (2.6 mL, 41.1 mmol) in DMF (40 mL) was added dropwise to the suspension. The reaction was warmed to -10°C and stirred for 3 h then quenched by addition of saturated ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was combined purified by silica gel column chromatography to give compound **5** (3.0 g, 68% yield). LC-MS: 320.3 (M+H), $C_{16}H_{18}ClN_3O_2$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.42 (s, 1H), 8.03 (s, 1H), 7.52 (s, 1H), 1.75 (s, 6H), 1.60 (s, 9H).

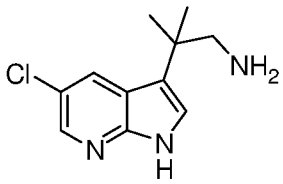
Step 6: 2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-methylpropanenitrile (6)



6

[00612] To a stirred solution of compound **5** (0.5 g, 1.57 mmol) in EA (4 mL) was added 3 N HCl/EA (4 mL). The reaction mixture was stirred at rt overnight then quenched by addition of aqueous $NaHCO_3$. The mixture was extracted with EA twice. The organics were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated to give compound **6** (0.33 g, 97% yield) as a light yellow oil, which was used in the next reaction without purification. LC-MS: 218.23 (M-H), $C_{11}H_{10}ClN_3$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 12.83 (br, 1H), 10.69 (br, 2H), 8.65 (s, 1H), 8.46 (s, 1H), 7.66 (s, 1H), 1.86 (s, 6H).

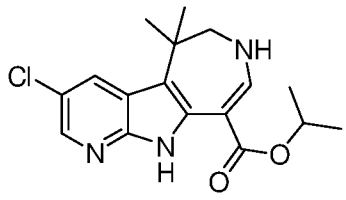
Step 7: 2-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-methylpropan-1-amine (7)



7

[00613] $LiAlH_4$ (120 mg, 3.13 mmol) was added in portions to a stirred solution of compound **6** (330 mg, 1.57 mmol) in THF (10 mL) at 0°C. The reaction was then heated at 70 °C and stirred for 5 h. The reaction mixture was then allowed to cool to rt and quenched with water. The mixture was acidified to pH 2-3 with 2 N HCl and washed with ethyl acetate. The water phase was basified to pH 8 with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated to give compound **7** (0.22 g, 66% yield), which was used in the next reaction without purification. LC-MS: 224.0 (M+H), $C_{11}H_{14}ClN_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.27 (br, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.15 (s, 1H), 2.95 (s, 2H), 1.39 (s, 6H).

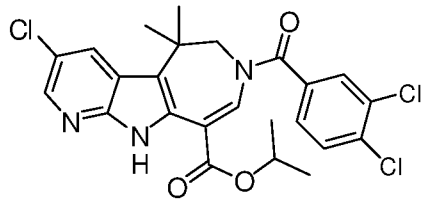
Step 8: Isopropyl 3-chloro-5,5-dimethyl-5,6,7,10-tetrahydropyrido [3',2':4,5] pyrrolo[2,3-d]azepine-9-carboxylate (8)



8

[00614] A mixture of compound **7** (160 mg, 0.71 mmol), isopropyl 3-bromo-2-oxopropanoate (300 mg, 1.43 mmol), and activated carbon (2 mg) in isopropanol (5 mL) was heated at 120°C for 1.2 h under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (PE/EA, from 20/1 to 10/1) to give compound **8** (52 mg, 22% yield) as a yellow solid. LC-MS: 334.32 (M+H), $C_{17}H_{20}ClN_3O_2$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.35 (br, 1H), 8.04 (br, 1H), 7.95 (br, 2H), 5.20-5.14 (m, 1H), 3.27 (br, 1H), 1.50 (s, 6H), 1.31 (d, J=6.0 Hz, 6H).

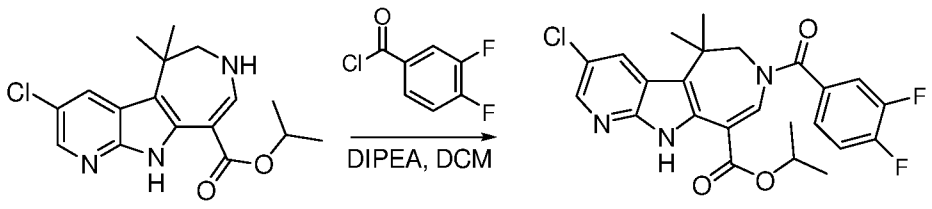
Step 9: Propan-2-yl 4-chloro-12-(3,4-dichlorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (9)



9

[00615] To a stirred solution of compound **8** (105 mg, 0.31 mmol) and DIPEA (0.55 mL, 3.10 mmol) in dichloromethane (5 mL), 3, 4-dichlorobenzoyl chloride (0.65 g, 3.10 mmol) in DCM (2 mL) was added. The reaction mixture was stirred at rt for 10 mins and it was then diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (PE/EA, from 20/1 to 10/1) to afford the title compound (130 mg, 81%) as a yellow solid. LC-MS: 508.20 (M+H), $C_{24}H_{22}Cl_3N_3O_3$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.17 (br, 1H), 8.23 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.73 (s, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 5.20-5.14 (m, 1H), 4.06 (br, 1H), 1.57 (s, 6H), 1.23 (d, J=6.0 Hz, 6H).

Example 2: Synthesis of propan-2-yl 4-chloro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (10)

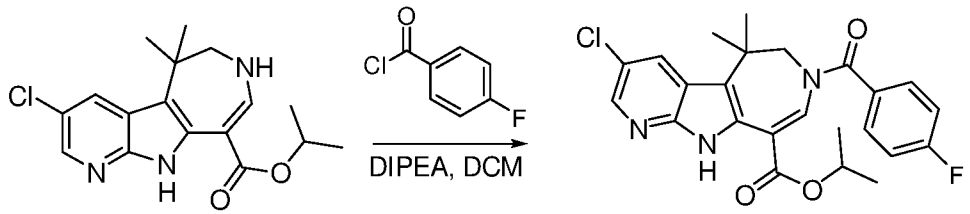


8 **10**

[00616] To a stirred solution of compound **8** (52 mg, 0.15 mmol) and DIPEA (0.13 mL, 0.75 mmol) in dichloromethane (4 mL), 3, 4-difluorobenzoyl chloride (0.09 mL, 0.75 mmol) in DCM (1 mL) was added. The reaction mixture was stirred at rt for 10 mins and it was then diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by silica gel

column chromatography (PE/EA, from 20/1 to 10/1) to afford the title compound (33 mg, 43%). LC-MS: 474.30 (M+H), $C_{24}H_{22}ClF_2N_3O_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ 11.10 (br, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.54-7.49 (m, 1H), 7.38-7.34 (m, 1H), 7.29-7.22 (m, 1H), 5.19-5.13 (m, 1H), 4.06 (br, 1H), 1.56 (s, 6H), 1.22 (d, J=6.4 Hz, 6H).

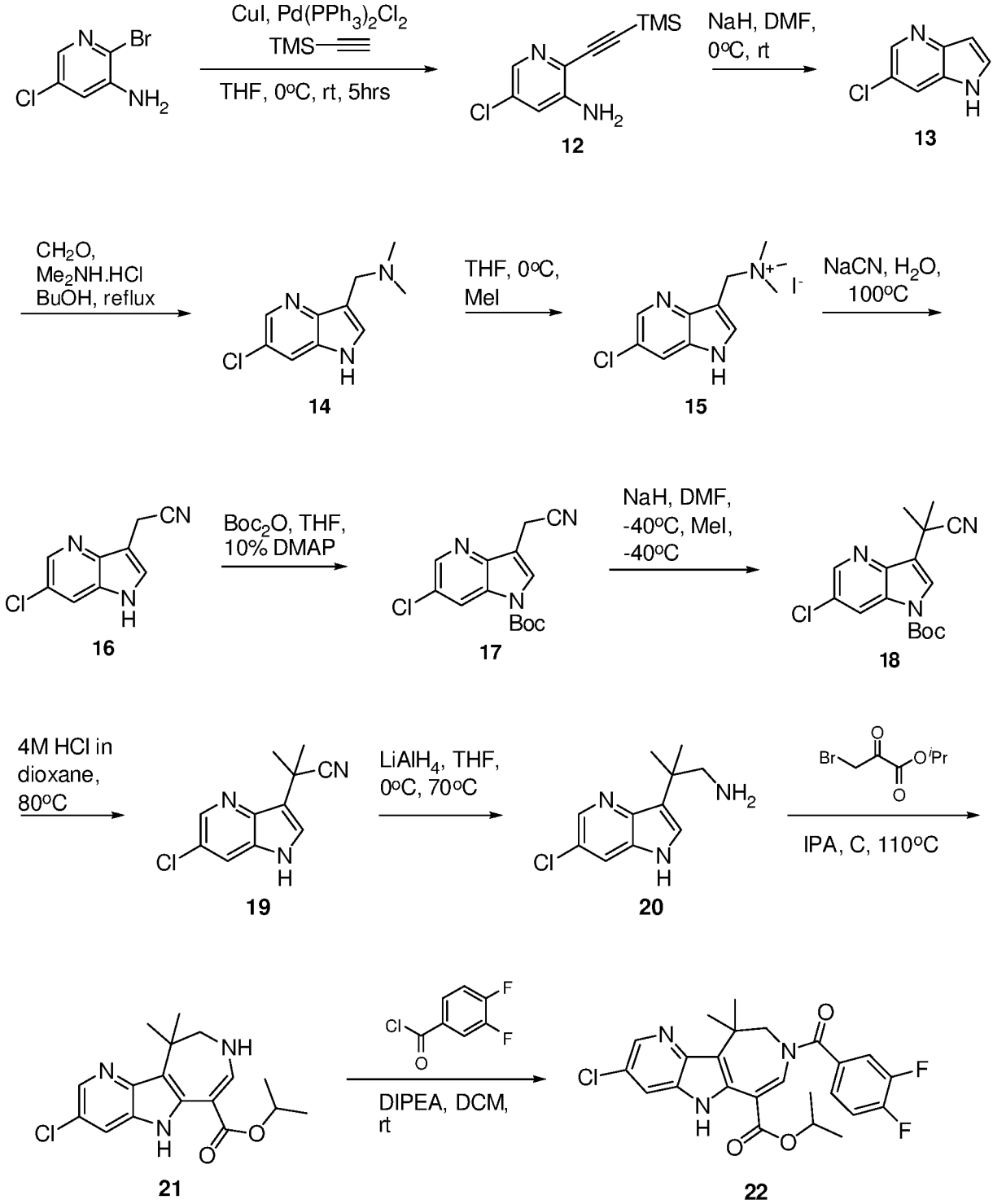
Example 3: Synthesis of propan-2-yl 4-chloro-12-(4-fluorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (11)



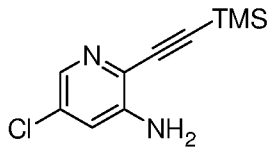
8 11

[00617] To a stirred solution of compound **8** (100 mg, 0.30 mmol) and DIPEA (0.52 mL, 3.0 mmol) in dichloromethane (5 mL), 4-fluorobenzoyl chloride (0.48 g, 3.0 mmol) in DCM (2 mL) was added. The reaction mixture was stirred at rt for 10 mins and it was then diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (PE/EA, from 20/1 to 10/1) to afford the title compound (100 mg, 73%) as a yellow solid. LC-MS: 456.41 (M+H), $C_{24}H_{23}ClFN_3O_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ 11.20 (br, 1H), 8.22 (s, 1H), 8.06 (s, 1H), 7.94 (s, 1H), 7.65-7.62 (m, 2H), 7.18-7.14 (m, 2H), 5.18-5.12 (m, 1H), 4.07 (br, 1H), 1.57 (s, 6H), 1.20 (d, J=6.0 Hz, 6H).

Example 4: Synthesis of propan-2-yl 5-chloro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (22)



Step 1: 5-Chloro-2-((trimethylsilyl)ethynyl)pyridin-3-amine (12)

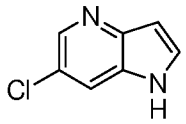


12

[00618] Ethynyltrimethylsilane (42.8 g, 0.44 mol) was added dropwise to a stirred mixture of 2-bromo-5-chloropyridin-3-amine (45 g, 0.22 mol), $Pd(PPh_3)_2Cl_2$ (15.5 g, 22 mmol), CuI (4.2 g, 22 mmol), and triethylamine (66 g, 0.66 mol) in THF (400 mL) at 0°C. The reaction mixture

was stirred for 5 h at rt under nitrogen. The mixture was diluted with water (1.2 L) and extracted with ethyl acetate (1 Lx3). The organic extracts were combined, washed with brine (300 mLx3), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give compound **12** (39 g, 80% yield). LC-MS: 225.01 (M+H), $C_{10}H_{13}ClN_2Si$. ^1H NMR (*$CDCl_3$*, 400 MHz) δ: 7.92 (s, 1H), 7.04 (s, 1H), 4.36 (br, 2H), 0.29 (s, 9H).

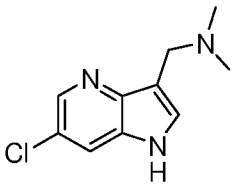
Step 2: 6-Chloro-1H-pyrrolo[3,2-b]pyridine (13)



13

[00619] Sodium hydride (34 g, 0.85 mol, 60% in mineral oil) was added in portions to a solution of compound **12** (38 g, 0.17 mol) in DMF (200 mL) at 0°C. The reaction was stirred for 5 h at rt under nitrogen. The mixture was poured into ice-water (500 mL) and extracted with ethyl acetate (500 mLx3). The organic extracts were combined, washed with brine (200 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give compound **13** (20 g, 78% yield). LC-MS: 153.14 (M+H), $C_7H_5ClN_2$. ^1H NMR (DMSO-d6, 400 MHz) δ 11.48 (br, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.70 (m, 1H), 6.59 (m, 1H).

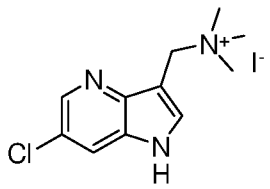
Step 3: 1-(6-Chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N-dimethylmethanamine (14)



14

[00620] Paraformaldehyde (3.26 g, 0.11 mol) and dimethylamine hydrochloride (8.85 g, 0.11 mol) were added to a solution of compound **13** (15 g, 98.7 mmol) in n-butanol (60 mL). The reaction was refluxed for 2 h. The solution was allowed to cool to rt and poured into 15% HCl (100 mL). The butanol layer was discarded and the water phase was adjusted to pH13-14 with 2M NaOH. The resulting mixture was extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated to give compound **14** (20 g, 97% yield), which was used in the next reaction without purification. LC-MS: 210.27 (M+H), $C_{10}H_{12}ClN_3$.

Step 4: 1-(6-Chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N,N-trimethylmethanaminium iodide (15)

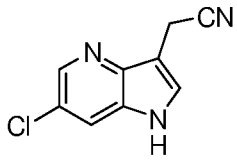


15

[00621] Iodomethane (67.9 g, 0.48 mol) was added dropwise to a stirred solution of compound **14** (20 g, 95.7 mmol) in THF (60 mL) at 0°C. The reaction was stirred for another 2 h at 0°C. The resulting precipitate was collected and washed with dichloromethane (30 mL) to give compound **15** (27 g, 80% yield), which was used in the next reaction without purification.

[00622] The compound was confirmed with LC-MS: 224.15 (M-I), $C_{11}H_{15}ClIN_3$.

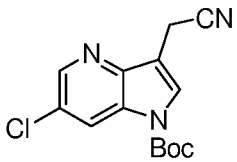
Step 5: 2-(6-Chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (16)



16

[00623] Sodium cyanide (8.4 g, 0.17 mol) was added to a stirred mixture of compound **15** (30 g, 85.5 mmol) in water (100 mL). The reaction mixture was stirred at 100°C for 1 h. The resulting precipitate was collected and the filtrate was extracted with ethyl acetate (100 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was combined with the collected solid to give compound **16** (15 g, 92% yield), which was used in the next reaction without purification. The compound was confirmed with LC-MS: 192.19 (M+H), $C_9H_6ClN_3$.

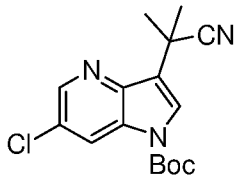
Step 6: tert-Butyl 6-chloro-3-(cyanomethyl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (17)



17

[00624] Boc_2O (27.4 g, 0.13 mmol) was added to a stirred solution of compound **16** (16 g, 83.8 mmol) and DMAP (1.36 g, 8.4 mmol) in THF (100 mL). The reaction mixture was stirred for another hour at rt. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to give compound **17** (17 g, 70% yield) as white solid. LC-MS: 292.32 (M+H), $C_{14}H_{14}ClN_3O_2$. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H), 8.45 (s, 1H), 7.90 (s, 1H), 3.92 (s, 2H), 1.70 (s, 9H).

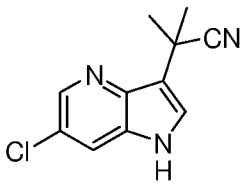
Step 7: *tert*-Butyl 6-chloro-3-(2-cyanopropan-2-yl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (18)



18

[00625] Sodium hydride (11.8 g, 0.29 mol, 60% in mineral oil) was added in portions to a stirred solution of compound **17** (17 g, 58.4 mmol) in DMF (60 mL) at -40°C (internal temperature was kept between -30°C and -40°C). The mixture was stirred for futher 10 min at this temperature and iodomethane (40 g, 0.28 mol) was added. The reaction mixture was then stirred for additional hour at -40°C. The reaction was quenched with ice water (200 mL) and extracted with ethyl acetate (200 mLx3). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was combined purified by silica gel column chromatography to give compound **18** (12 g, 64% yield). LC-MS: 320.30 (M+H), $C_{16}H_{18}ClN_3O_2$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 8.43 (s, 1H), 7.81 (s, 1H), 1.95 (s, 2H), 1.70 (s, 9H).

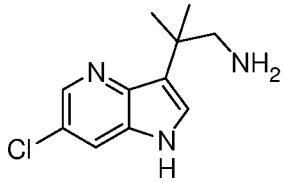
Step 8: 2-(6-Chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (19)



19

[00626] A solution of compound **18** (0.5 g, 1.6 mmol) in 4 N HCl/dioxane (mL) was heated at 80°C for 3 h. The solvent was removed in vacuo. The residue was dissolved in water (20 mL) and basified to pH 9 with saturated sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate (20 mLx3). The organic extracts were combined, washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated to give compound **19** (0.33 g, 96% yield), which was used in the next reaction without purification. LC-MS: 220.23 (M+H), $C_{11}H_{10}ClN_3$.

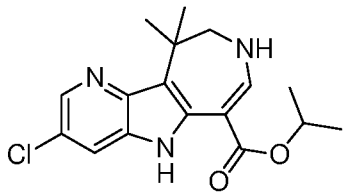
Step 9: 2-(6-Chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropan-1-amine (20)



20

[00627] $LiAlH_4$ (76 mg, 2 mmol) was added in portions to a stirred solution of compound **19** (219 mg, 1 mmol) in THF (10 mL) at 0°C. The reaction was stirred at 70 °C for 2 h. The reaction mixture was allowed to cool to rt and quenched with water (0.5 mL). The mixture was acidified to pH 2-3 with 2 N HCl and washed with ethyl acetate (5 mL). The aqueous phase was basified to pH 8 with saturated sodium bicarbonate solution and extracted with ethyl acetate (5 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated to give compound **20** (0.2 g, 90% yield, containing ~20% de-chloro product), which was used in the next reaction without purification. LC-MS: 224.33 (M+H), $C_{11}H_{14}ClN_3$.

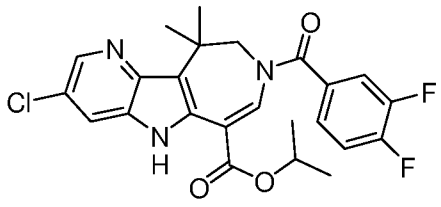
Step 10: Isopropyl 3-chloro-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (21)



21

[00628] A mixture of compound **20** (50 mg, 0.22 mmol), isopropyl 3-bromo-2-oxopropanoate (93 mg, 0.45 mmol), and activated carbon (2 mg) in isopropanol (5 mL) was heated at 110°C for 30 min under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. Another batch of microwave irradiation was carried out with compound **20** (150 mg, 0.67 mmol), isopropyl 3-bromo-2-oxopropanoate (442 mg, 2.7 mmol), and activated carbon (5 mg) for an hour at 110°C. The crude materials of two batches were combined and purified by silica gel column chromatography, then prep-HPLC to give compound **21** (90 mg, 30% yield). The compound was confirmed with LC-MS: 334.04 (M+H), $C_{17}H_{20}ClN_3O_2$.

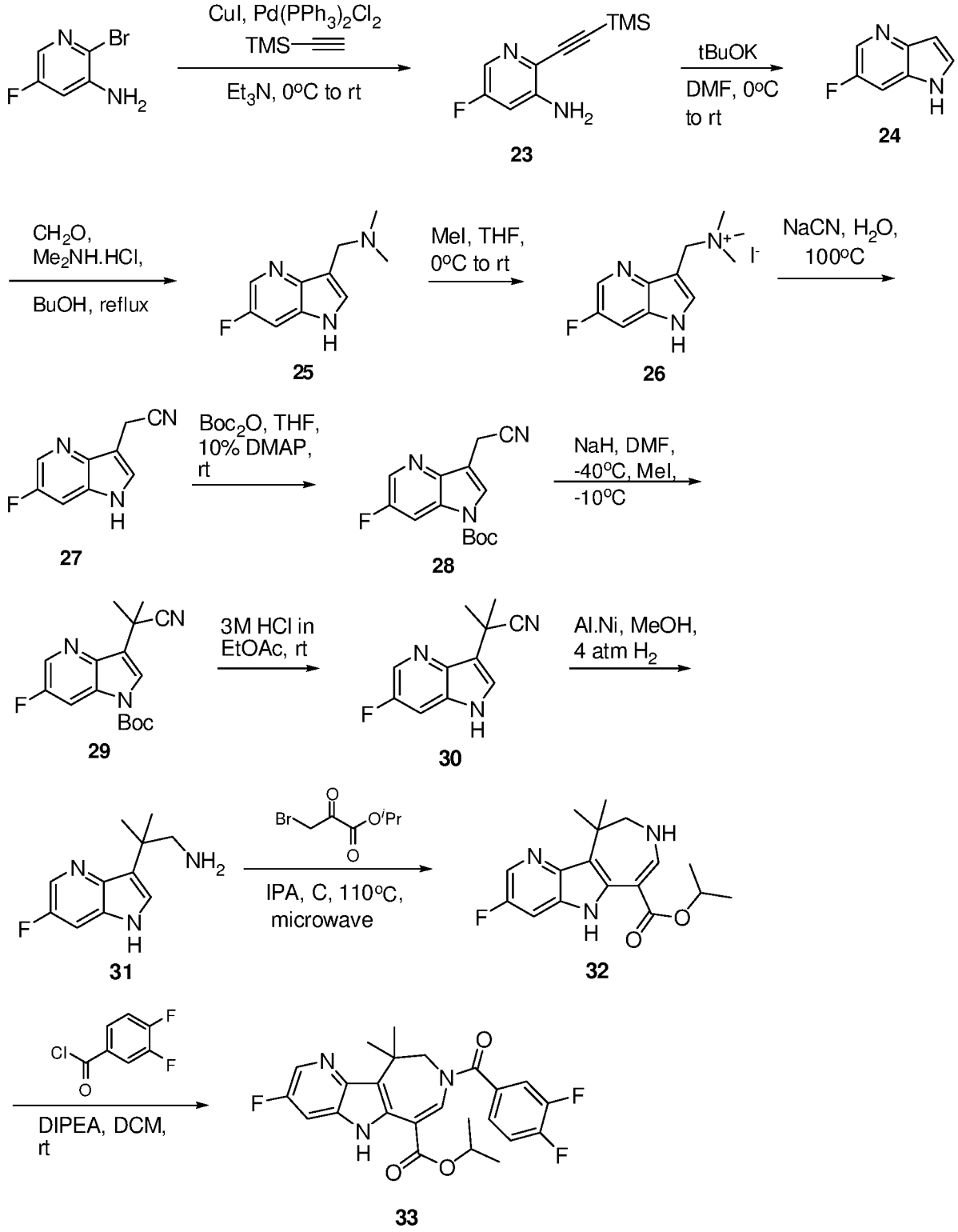
Step 11: Propan-2-yl 5-chloro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (22)



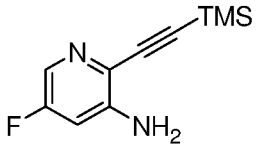
22

[00629] 3, 4-Difluorobenzoyl chloride (37 mg, 0.21 mmol) and DIPEA (27 mg, 0.21 mmol) were added to a stirred solution of compound **21** (10 mg, 0.03 mmol) in dichloromethane (0.5 mL) at rt and the final reaction mixture was stirred for 30 min at rt. Another batch of acylation was carried out with compound **21** (80 mg, 0.24 mmol). The two batches were combined and concentrated in vacuo. The residue was purified by silica gel column chromatography and then by prep-HPLC and washed with petroleum/ethyl acetate (20:1, 1 mLx3) to afford the title product, compound **22** (25 mg, 19% yield). LC-MS: 474.81 (M+H), $C_{24}H_{22}ClF_2N_3O_3$. ^1H NMR (*$CDCl_3$*, 400 MHz) *δ*: 10.88 (br, 1H), 8.39 (s, 1H), 7.93 (s, 1H), 7.62 (s, 1H), 7.54-7.49 (m, 1H), 7.39-7.36 (m, 1H), 7.29-7.23 (m, 1H), 5.19-5.12 (m, 1H), 4.05 (br, 1H), 1.71 (s, 6H), 1.23 (d, *J*=6.0 Hz, 6H).

Example 5: Synthesis of propan-2-yl 5-fluoro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (33)



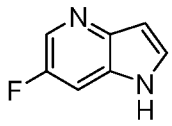
Step 1: 5-Fluoro-2-((trimethylsilyl)ethynyl)pyridin-3-amine (23)



23

[00630] Ethynyltrimethylsilane (0.82 mL, 6.3 mmol) was added dropwise to a stirred mixture of 2-bromo-5-fluoropyridin-3-amine (1.0 g, 5.23 mmol), $Pd(PPh_3)_2Cl_2$ (0.18 g, 0.26 mmol) and CuI (50 mg, 0.26 mmol) in triethylamine (15 mL) at 0°C. The reaction was stirred for 4 h at rt under nitrogen. The mixture was concentrated under reduce pressure. The residue was purified by silica gel column chromatography (PE/EA, from 20/1 to10/1) to give compound **23** (0.8 g, 73% yield). LC-MS: 209.16 (M+H), $C_{10}H_{13}FN_2Si$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.83 (s, 1H), 6.75-6.72 (m, 1H), 4.40 (br, 2H), 0.28 (s, 9H).

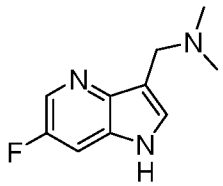
Step 2: 6-Fluoro-1H-pyrrolo[3,2-b]pyridine (24)



24

[00631] *t*-BuOK (11.3 g, 101 mmol) was added to a stirred solution of compound **23** (7.5 g, 33.65 mmol) in DMF (100 mL) at 0°C. The reaction was stirred for 2 h at rt under nitrogen. The mixture was poured into ice-water (100 mL) and extracted with ethyl acetate (200 mLx3). The organic extracts were combined, washed with brine (200 mLx2), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography to give compound **24** (3.7 g, 75% yield). LC-MS: 137.11 (M+H), $C_7H_5FN_2$. ^1H NMR (*$CDCl_3$*, 400 MHz) δ: 7.85 (s, 1H), 6.75-6.72 (m, 1H), 4.41 (br, 2H).

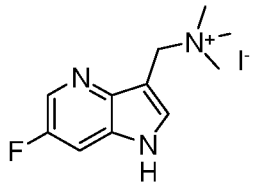
Step 3: 1-(6-Fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N-dimethylmethanamine (25)



25

[00632] Paraformaldehyde (0.24 g, 8.1 mmol) and dimethylamine hydrochloride (0.66 g, 8.1 mmol) were added to a stirred solution of compound **24** (1.0 g, 7.35 mmol) in *n*-butanol (10 mL). The reaction was refluxed for 3 h. The solution was allowed to cool to rt and poured into 15% HCl (100 mL). The butanol layer was discarded and the water phase was adjusted to pH13-14 with 2M NaOH. The resulting mixture was extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give compound **25** (1.0 g, 71% yield), which was used in the next reaction without purification. LC-MS: 194.02 (M+H), $C_{10}H_{12}FN_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 10.13 (br, 1H), 8.36 (s, 1H), 7.31-7.22 (m, 2H), 3.75 (s, 2H), 2.32 (s, 6H).

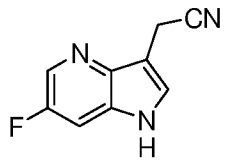
Step 4: 1-(6-Fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N,N-trimethylmethanaminium iodide (26)



26

[00633] Iodomethane (0.81 mL, 13.0 mmol) was added dropwise to a stirred solution of compound **25** (1.0 g, 5.2 mmol) in THF (20 mL) at 0°C. The reaction was stirred at rt overnight. The resulting precipitate was collected and dried to give compound **26** (1.3 g, 76% yield), which was used in the next reaction without purification. LC-MS: 208.25 (M+), $C_{11}H_{15}FIN_3$. ^{1}H NMR (D_2O, 400 MHz) δ: 8.11 (s, 1H), 7.83 (s, 1H), 7.55-7.52 (m, 1H), 4.56 (s, 2H), 3.15 (s, 3H), 3.04 (s, 6H).

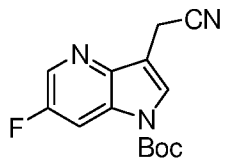
Step 5: 2-(6-Fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (27)



27

[00634] Sodium cyanide (0.37 g, 7.6 mmol) was added to a stirred solution of compound **26** (1.3 g, 3.8 mmol) in water (30 mL). The reaction mixture was stirred for 2 h at 100°C, then, allowed to cool. The mixture was extracted with ethyl acetate (50 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated to give compound **27** (0.24 g, 36% yield), which was used in the next reaction without purification. LC-MS: 174.04 (M-H), $C_9H_6FN_3$. ^{1}H NMR (DMSO, 300 MHz) δ: 11.47 (br, 1H), 8.38 (s, 1H), 7.73-7.68 (m, 2H), 4.03 (s, 2H).

Step 6: *tert*-Butyl 6-fluoro-3-(cyanomethyl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (28)

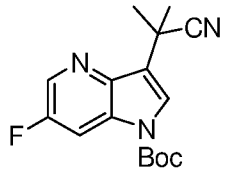


28

[00635] Boc_2O (0.28 g, 1.3 mmol) was added to a stirred solution of compound **27** (0.24 g, 1.37 mmol) and DMAP (17 mg, 0.14 mmol) in THF (10 mL). The mixture was stirred for 10 min at rt. The reaction was quenched by addition of citric acid (10%). The resulting mixture was extracted with ethyl acetate. The organics extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography to give compound **28** (0.33 g, 88% yield) as a white solid. LC-MS: 276.0 (M+H), $C_{14}H_{14}FN_3O_2$. ^{1}H NMR ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.45 (s, 1H), 8.16 (br, 1H), 7.90 (s, 1H), 3.93 (s, 2H), 1.70 (s, 9H).

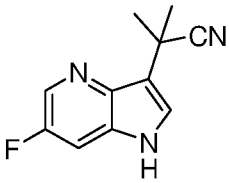
Step 7: *tert*-Butyl 6-fluoro-3-(2-cyanopropan-2-yl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (29)



29

[00636] A suspension of sodium hydride (120 mg, 3.0 mmol, 60% in mineral oil) in DMF (10 mL) was cooled to -40°C under nitrogen. A mixture of compound **28** (330 mg, 1.2 mmol) and iodomethane (0.22 mL, 3.6 mmol) in DMF (10 mL) was added dropwise. The mixture was allowed to warm to -10°C and stirred for 4 h, then quenched by addition of saturated ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was combined purified by silica gel column chromatography to give compound **29** (0.29 g, 80% yield). LC-MS: 304.36 (M+H), $C_{16}H_{18}FN_3O_2$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.46 (s, 1H), 8.13 (br, 1H), 7.79 (s, 1H), 1.94 (s, 6H), 1.68 (s, 9H).

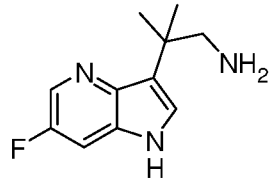
Step 8: 2-(6-Fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (30)



30

[00637] To a stirred solution of compound **29** (0.24 g, 0.95 mmol) in EA (3 mL) was added 3 N HCl/EA (3 mL). The reaction was stirred at rt overnight then concentrated. LCMS showed a mixture of product and starting material. Another portion of HCl/EA (5 mL) was added and the reaction was stirred at rt for further 5 h then concentrated again. The residue was slurried in EA (5 mL) for 0.5 h then filtered. The cake was dried under vacuum to give compound **30** (0.18 g, 93% yield) as a white solid, which was used in the next reaction without purification. LC-MS: 204.04 (M+H), $C_{11}H_{10}FN_3$. ^{1}H NMR (*DMSO*, 300 MHz) δ: 11.68 (br, 1H), 8.44 (s, 1H), 7.79-7.75 (m, 1H), 7.67 (s, 1H), 1.84 (s, 6H).

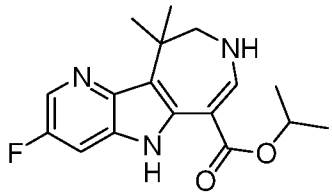
Step 9: 2-(6-Fluoro-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropan-1-amine (31)



31

[00638] A solution of compound **30** (0.20 g) in methanol (100 mL) with Raney nickel (0.2g in water) was hydrogenated in Parr hydrogenator (4 atm) at rt overnight. The solid was filtered off and the filtrate was concentrated to afford compound **31** as a light yellow solid (0.20g, quantitative), which was used in the next reaction without purification. LC-MS: 208.04 (M+H), $C_{11}H_{14}FN_3$. ^{1}H NMR (DMSO, 300 MHz) δ 11.45 (br, 1H), 8.34 (s, 1H), 7.90 (br, 2H), 7.70-7.66 (m, 1H), 7.47 (s, 1H), 3.27 (s, 2H), 1.47 (s, 6H).

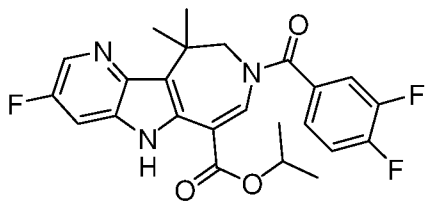
Step 10: Isopropyl 3-c fluoro-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (32)



32

[00639] A mixture of compound **31** (80 mg, 0.48 mmol), isopropyl 3-bromo-2-oxopropanoate (130 mg, 0.72 mmol), and activated carbon (2 mg) in isopropanol (4 mL) was heated at 110°C for 2 h under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (PE/EA, 20/1 then DCM/CH_3OH, 20/1), followed by MS-triggered prep-HPLC to give compound **32** (90 mg, 34% yield) as yellow solid. LC-MS: 318.41 (M+H), $C_{17}H_{20}FN_3O_2$. ^{1}H NMR (*CDCl*$_3$, 300 MHz) δ: 11.23 (br, 1H), 8.26 (s, 1H), 77.97 (br, 1H), 7.28 (s, 1H), 5.66 (br, 1H), 5.21-5.13 (m, 1H), 3.29 (br, 2H), 1.65 (s, 6H), 1.34 (d, *J*=6.0 Hz, 6H).

Step 11: Propan-2-yl 5-fluoro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (33)

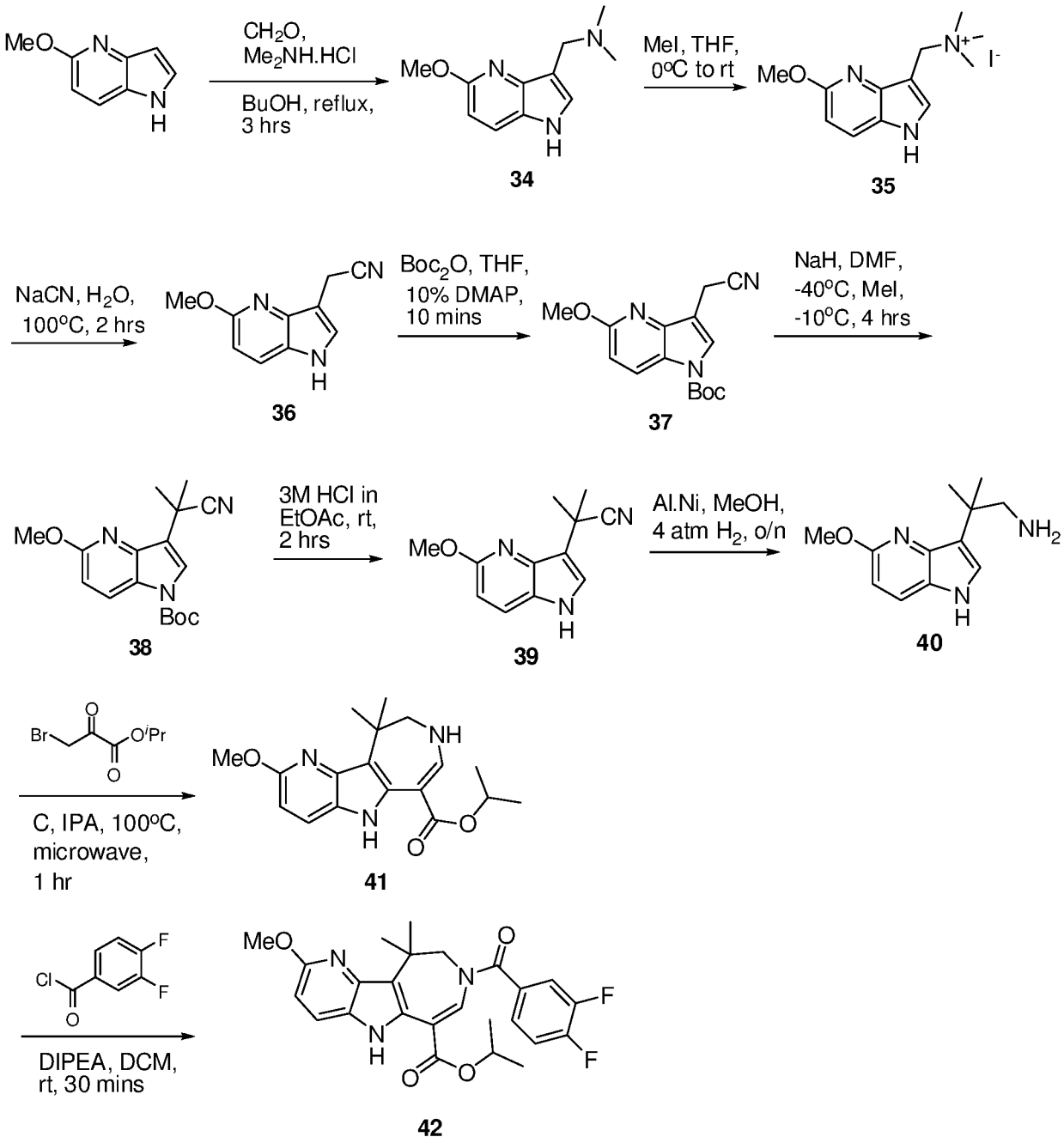


33

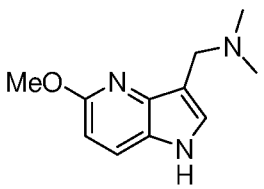
[00640] 3, 4-Difluorobenzoyl chloride a stirred solution of compound **32** (40 mg, 0.126 mmol) and DIPEA (0.20 mL, 1.26 mmol) in dichloromethane (4 mL), 3, 4-difluorobenzoyl chloride

(0.14 mL, 1.26 mmol) in DCM (1 mL) was added. The reaction mixture was stirred for 30 min at rt. Another batch of acylation reaction was carried out with compound **32** (15 mg, 0.047 mmol). The two batches were combined, washed with saturated NaHCO3 solution and brine. The organics were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford a yellow solid, which was slurried in a mixture of PE/EA (2 mL, 20/1) to give the title compound (25 mg, 31%). LC-MS: 458.40 (M+H), $C_{24}H_{22}F_3N_3O_3$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.86 (br, 1H), 8.36 (s, 1H), 8.88 (s, 1H), 7.53-7.48 (m, 1H), 7.39-7.22 (m, 3H), 5.18-5.12 (m, 1H), 4.11 (br, 1H), 1.71 (s, 6H), 1.23 (d, J=6.0 Hz, 6H).

Example 6: Synthesis of propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-4-methoxy-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (42)



Step 1: 1-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N-dimethylmethanamine (34)

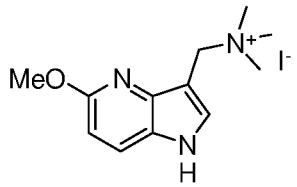


34

[00641] Paraformaldehyde (0.22 g, 7.43 mmol) and dimethylamine hydrochloride (0.61 g, 7.43 mmol) were added to a stirred solution of 5-methoxy-1H-pyrrolo[3,2-b]pyridine (1.0 g, 6.76 mmol) in *n*-butanol (10 mL). The reaction was refluxed for 3 h. The solution was allowed to cool to rt and quenched by addition of saturated $NaHCO_3$ solution. The resulting mixture was extracted with ethyl acetate (100 mLx3). The organic extracts were combined, washed with

brine (100 mL), dried over anhydrous sodium sulfate, and concentrated to give compound **34** (1.22 g, 88% yield), which was used in the next reaction without purification. LC-MS: 206.24 (M+H), $C_{11}H_{15}N_3O$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.73 (br, 1H), 7.52 (s, 1H), 7.25 (s, 1H), 6.63-6.56(m, 1H), 4.00 (s, 3H), 3.75 (s, 2H), 2.35(s, 6H).

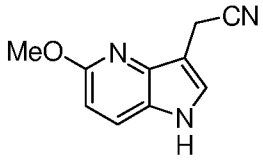
Step 2: 1-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)-N,N,N-trimethylmethanaminium iodide (35)



35

[00642] Iodomethane (0.93 mL, 14.9 mmol) was added dropwise to a stirred solution of compound **34** (1.22 g, 5.95 mmol) in THF (30 mL) at 0°C. The reaction was stirred at rt overnight. The resulting precipitate was collected and dried to give compound **35** (1.4 g, 70% yield), which was used in the next reaction without purification. LC-MS: 347.0 (M+H), $C_{12}H_{18}IN_3O$. ^{1}H NMR (D_2O, 400 MHz) δ: 7.78(br, 1H), 7.67 (br, 1H), 6.67 (br, 1H), 4.54 (s, 2H), 3.86 (s, 3H), 3.11 (m, 9H).

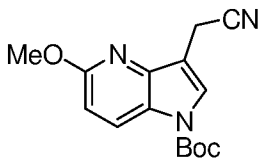
Step 3: 2-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (36)



36

[00643] Sodium cyanide (0.40 g, 8.06 mmol) was added to a stirred solution of compound **2** (1.4 g, 4.03 mmol) in water (40 mL). The reaction was stirred for 2 h at 100°C then cooled. The mixture was extracted with ethyl acetate (50 mLx3). The organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash chromatography (PE/EA, 5/1) give compound **3**(0.45 g, 60% yield) as a white solid. LC-MS: 188.22 (M+H), $C_{10}H_9N_3O$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14 (br, 1H), 7.57 (s, 1H), 7.36 (s, 1H), 6.65(s, 1H), 3.99 (s, 3H), 3.91 (d, 2H).

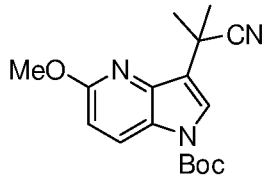
Step 4: *tert*-Butyl 5-methoxy-3-(cyanomethyl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (37)



37

[00644] Boc_2O (0.52 g, 2.4 mmol) was added to a stirred solution of compound **36** (0.45 g, 2.4 mmol) and DMAP (29 mg, 0.24 mmol) in THF (10 mL). The reaction was stirred for 10 min at rt. The reaction was quenched by addition of citric acid (10%). The resulting mixture was extracted with ethyl acetate. The organics were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give compound **37** (0.55 g, 80% yield) as white solid. LC-MS: 288.41(M+H), $C_{15}H_{17}N_3O_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.14 (br, 1H), 7.57(s, 1H), 7.36(s, 1H), 6.66-6.64 (m, 1H), 3.99 (s, 3H), 3.91 (s, 2H).

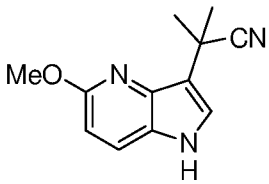
Step 5: *tert*-Butyl 5-methoxy-3-(2-cyanopropan-2-yl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (38)



38

[00645] A suspension of sodium hydride (191 mg, 4.8 mmol, 60% in mineral oil) in DMF (10 mL) was allowed to cool to -40°C under nitrogen. A mixture of compound **37** (550 mg, 1.9 mmol) and iodomethane (0.35 mL, 5.7 mmol) in DMF (10 mL) was added dropwise. The reaction mixture was allowed to warm to -10°C and stirred for 4 h then quenched by addition of saturated ammonium chloride solution. The resulting mixture was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography to give compound **38** (0.43 g, 71% yield). LC-MS: 316.40 (M+H), $C_{17}H_{21}N_3O_3$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br, 1H), 7.55 (m, 1H), 7.29 (m, 1H), 6.72-6.70 (m, 1H), 3.98 (s, 3H), 1.96 (s, 6H), 1.66 (s, 6H).

Step 6: 2-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (39)

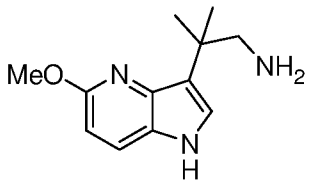


39

[00646] To a stirred solution of compound **38** (0.43 g, 1.36 mmol) in EA (2 mL) was added 3 N HCl/EA (10 mL). The reaction was stirred at rt for 2 h then quenched by addition of aqueous $NaHCO_3$. The mixture was extracted with EA twice. The organics were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated to give compound **39** (0.28 g, 95% yield) as a light yellow oil, which was used in the next reaction without purification. LC-MS:

215.96 (M+H), $C_{12}H_{13}N_3O$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (br, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.29 (s, 1H), 6.62 (d, J=8.8 Hz, 1H), 3.99 (s, 3H), 1.96 (s, 6H).

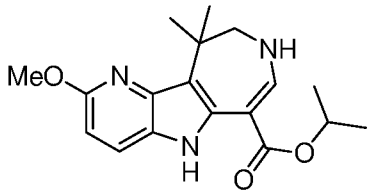
Step 7: 2-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropan-1-amine (40)



40

[00647] A stirred solution of compound **39** (0.28 g) in methanol (100 mL) with Raney nickel (0.2g in water) was hydrogenated in Parr hydrogenator (4 atm) at rt overnight then filtered. The filtrate was concentrated to afford compound **40** as a light yellow solid (0.28 g, quantitative), which was used in the next reaction without purification. LC-MS: 220.29 (M+H), $C_{12}H_{17}N_3O$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.87 (br, 1H), 7.64-7.61 (m, 1H), 7.17 (s, 1H), 6.49 (s, 1H), 3.87 (s, 3H), 2.89 (s, 2H), 1.36 (s, 6H).

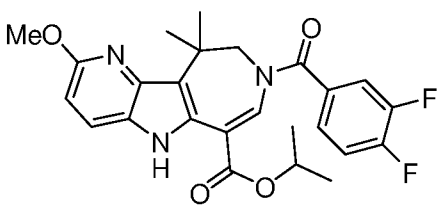
Step 8: Isopropyl 2-methoxy-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (41)



41

[00648] A mixture of compound **40** (330 mg, 1.51 mmol), isopropyl 3-bromo-2-oxopropanoate (472 mg, 2.27 mmol), and activated carbon (2 mg) in isopropanol (20 mL) was heated at 100°C for 1 h under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography, followed by MS-triggered prep-HPLC to give compound **41** (10 mg, 34% yield) as a yellow solid. LC-MS: 330.38 (M+H), $C_{18}H_{23}N_3O_3$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.87 (br, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 6.37 (br, 1H), 5.11-5.04 (m, 1H), 3.90 (s, 3H), 3.30 (br, 2H), 1.57 (br, 6H), 1.26 (d, J=6.0 Hz, 6H).

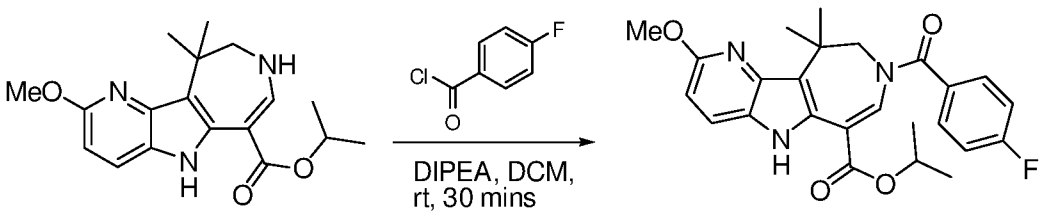
Step 9: Propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-4-methoxy-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (42)



42

[00649] To a stirred solution of compound **41** (47 mg, 0.143 mmol) and DIPEA (0.25 mL, 1.43 mmol) in dichloromethane (4 mL), 3, 4-difluorobenzoyl chloride (0.08 mL, 0.714 mmol) in DCM (1 mL) was added. The reaction was stirred for 30 min at rt, then diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to afford a yellow solid, which was further purified by preparative TLC to give the title compound (25 mg, 37%). LC-MS: 470.40 (M+H), $C_{25}H_{25}F_2N_3O_4$. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.67 (br, 1H), 7.81 (s, 1H), 7.57-7.49 (m, 2H), 7.39-7.36 (m, 1H), 7.27-7.21 (m, 1H), 6.60 (d, J=6.0 Hz, 8.4H), 5.17-5.11 (m, 1H), 4.00 (br, 4H), 1.71 (s, 6H), 1.23 (d, J=6.4 Hz, 6H).

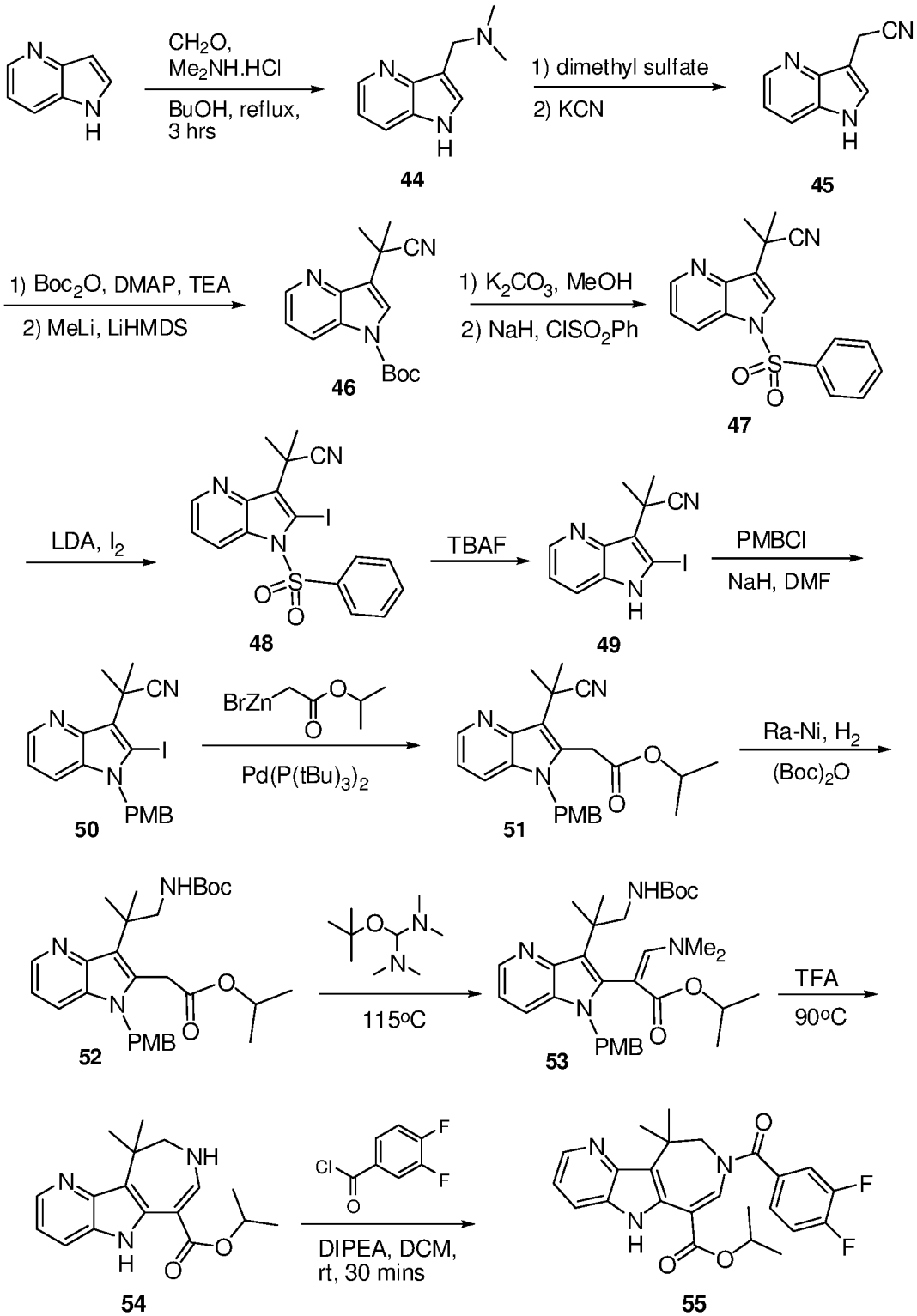
Example 7: Synthesis of propan-2-yl 12-(4-fluorobenzoyl)-14,14-dimethyl-4-methoxy-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (43)



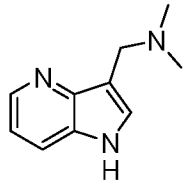
41 **43**

[00650] To a stirred solution of compound **41** (56 mg, 0.17 mmol) and DIPEA (0.30 mL, 1.70 mmol) in dichloromethane (4 mL), 4-fluorobenzoyl chloride (135 mg, 0.85 mmol) in DCM (2 mL) was added. The reaction was stirred for 30 min at rt, then diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine. The organics were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 100/1 to 50/1 then 30/1) to afford the title compound (30 mg, 39%) as a yellow solid. LC-MS: 452.44 (M+H), $C_{25}H_{26}FN_3O_4$. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.78 (br, 1H), 7.87 (s, 1H), 7.66-7.62 (m, 2H), 7.58 (d, J=8.4 Hz, 1H), 7.15 (t, J=8.4 Hz, 1H), 6.60 (d, J=8.4 Hz, 1 H), 5.16-5.09 (m, 1H), 4.02 (br, 4H), 1.73 (s, 6H), 1.20 (d, J=6.0 Hz, 6H).

Example 8: Synthesis of propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (55)



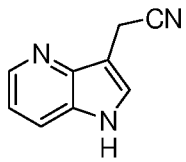
Step 1: N,N-Dimethyl-1-(1H-pyrrolo[3,2-b]pyridin-3-yl)methanamine (44)



44

[00651] To a solution of 1,4-azaindole (8.7 g, 1.0 eq.) in n-butanol (100 mL) was added formaldehyde (6.6 g. 37% in water, 1.1 eq.) and dimethylamine hydrochloride salt (6.6 g, 1.1 eq.). The resulting mixture was heated at reflux for 3h. The mixture was cooled and the solvent was removed in vacuo. The mixture was diluted with 100 mL ethyl acetate, washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo to provide compound **44** (13 g) which was used without further purification.

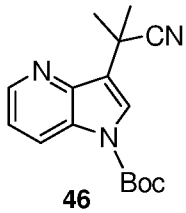
Step 2: 2-(1H-Pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (45)



45

[00652] To a solution of compound **44** (13g, 1.0eq.) in THF (100 mL) was added dropwise dimethyl sulfate (9.3 g, 1.0 eq.). The resulting mixture was heated at reflux for 30 minutes. The solvent was removed, and the residue was dissolved in 80 mL water. To the mixture was added KCN (5.3 g, 1.1 eq.) and the mixture was refluxed for 3h. The reaction was cooled to room temperature and extracted from ethyl acetate (3 x 40 mL). The combined organic layers were concentrated in vacuo to afford compound **45** (8.3 g) which was used without purification.

Step 3: tert-Butyl 3-(2-cyanopropan-2-yl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (46)

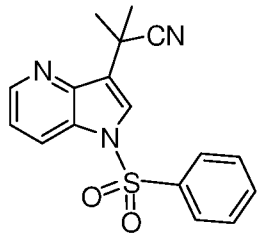


46

[00653] To a solution of compound **45** (8.3 g, 1.0 eq.) in CH_2Cl_2 (50 mL) was added di-tert-butyl dicarbonate (12.7 g, 1.1 eq.), DMAP (100 mg), and triethyl amine (8.1 g, 1.5 eq.). The reaction mixture was stirred at room temperature for 2.5h. The mixture was washed with NH_4Cl, and brine to afford n-Boc protected intermediate (13.5 g). To a solution of intermediate (13.5 g) and CH_3I (22.5 g, 3.0 eq) in dry THF (100 mL) at -78°C under N_2 was added LiHMDS (158 mL, 1M in THF, 3.0 eq.) dropwise over 30 minutes. The resulting mixture was stirred at -78°C for 20 minutes then gradually warmed to 0°C over 2h. The reaction was quenched by saturated NH_4Cl,

and then extracted from ethyl acetate (2 x 150 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo to provide compound **46** (16.7 g) which was used without further purification.

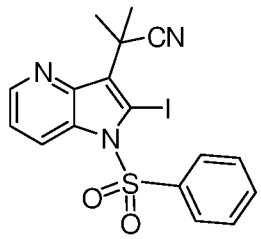
Step 4: 2-Methyl-2-(1-(phenylsulfonyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)propanenitrile (47)



47

[00654] To a solution of compound **46** (16.7 g, 1.0 eq) in MeOH (100 mL) was added K_2CO_3 (40 g, 5.0 eq). The mixture was heated at 60°C for 1hr. The inorganic salt was removed by filtration and the filtrate was diluted with 250 mL ethyl acetate, washed with water and brine and concentrated to provide intermediate (10.8 g). To a solution of the intermediate (10.8 g, 1.0 eq) in dry THF (100 mL) at 0°C was added NaH (3.5 g, 60%, 1.5 eq.). The reaction mixture was stirred at 0°C for 30 minutes and then benzenesulfonyl chloride (11.4 g, 1.1 eq.) in THF (20 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1h. The reaction was quenched with ice-water and extracted from ethyl acetate (3 x 125 mL). The combined organic layers were concentrated in vacuo and the residue was purified by column chromatography to provide compound **47** (7.3 g).

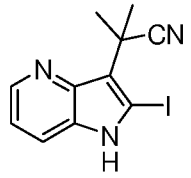
Step 5: 2-(2-Iodo-1-(phenylsulfonyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (48)



48

[00655] LDA (45 mL, 1M in THF, 2.0 eq.) was added dropwise to a solution of compound **47** (7.3 g, 1.0 eq.) in dry THF (50 mL) at -78°C under N_2. The mixture was stirred at -78°C for 30 minutes. I_2 (11.4 g, 2.0 eq.) was added to the reaction mixture. The resulting mixture was stirred at -78°C for 5 minutes then warmed to 0°C in one hour. The reaction was quenched by saturated NH_4Cl, washed with 10% $Na_2S_2O_5$ (30 mL), and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to provide compound **48** (10.1 g) which was used without further purification.

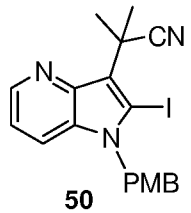
Step 6: 2-(2-Iodo-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (49)



49

[00656] To a solution of compound **48** (7.9 g, 1.0 eq.) in THF (10 mL), was added TBAF (88 mL, 1M in THF, 5.0 eq.). The resulting mixture was stirred at room temperature for 1h. The solvent was removed in vacuo. The residue was dissolved in 100 mL ethyl acetate, washed with saturated NH_4Cl, water and brine. The solvent was concentrated in vacuo to provide compound **49** (5.4 g) which was used without further purification.

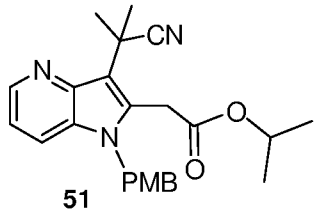
Step 7: 2-(2-iodo-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (50)



50

[00657] To a solution of compound **49** (5.4 g, 1.0 eq) in dry THF (50 mL), was added NaH (2.2 g, 60%, 3.0 eq.) at 0°C under N_2. The mixture was stirred at room temperature for 30 minutes, and then p-methoxybenzyl chloride (3.3 g, 1.2 eq.) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 2h. The reaction was quenched with saturated NH_4Cl, washed with water and brine. The crude mixture was purified by column chromatography to afford compound **50** (5.2 g, 69.5%).

Step 8: Isopropyl 2-(3-(2-cyanopropan-2-yl)-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridin-2-yl)acetate (51)

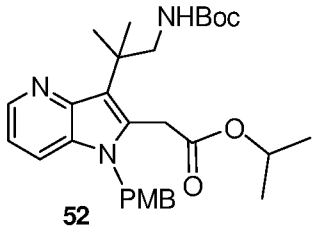


51

[00658] To a solution of compound **50** (1.7 g, 1.0 eq.) in dry THF (50 mL), was added $Pd(P(tBu)_3)_2$ (1.7 g). The mixture was flushed with nitrogen for 5 minutes. A solution of (2-isopropoxy-2-oxoethyl) zinc bromide in THF (21 mL, ~0.3M, 1.6 eq.) was added dropwise under N_2. The resulting mixture was stirred in an oil bath, temperature starting from room temperature to 70 °C within 10 minutes, and then the reaction was heated at 70 °C for 1h. The reaction mixture was cooled to room temperature and quenched with 60 mL saturated NH_4Cl.

The crude mixture was purified by column chromatography to provide compound **51** (1.5 g, 93.4%).

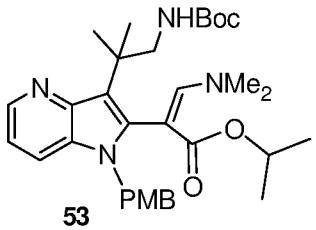
Step 9: Isopropyl 2-(3-(1-(tert-butoxycarbonylamino)-2-methylpropan-2-yl)-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridin-2-yl)acetate (52)



52

[00659] To a solution of compound **51** (1.5 g, 1.0 eq.) in THF (20 mL) and iPrOH (30 mL), was added Boc anhydride (1.6 g, 2.0 eq.), 8 mL Ra-Ni in water, and a few drops of saturated NH_4OH. The resulting mixture was hydrogenated at H_2 40 psi for 5 h. The catalyst was carefully removed by filtration. The solvent was concentrated in vacuo and the residue was purified by column chromatography to give compound **52** (1.6 g, 84%).

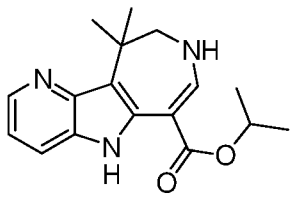
Step 10: Isopropyl 2-(3-(1-(tert-butoxycarbonylamino)-2-methylpropan-2-yl)-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridin-2-yl)-3-(dimethylamino)acrylate (53)



53

[00660] A solution of compound **52** (1.6 g) in 1-tert-butoxy-N,N,N',N'-tetramethylmethanediamine (8 mL) was flushed with nitrogen and then heated at 115 °C in a sealed-tube for 4h. The mixture was cooled to room temperature, diluted with 100 mL CH_2Cl_2, washed with water and brine. The crude mixture was purified by column chromatography to give compound **53** (1.52 g, 85%).

Step 11: Isopropyl 10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (54)

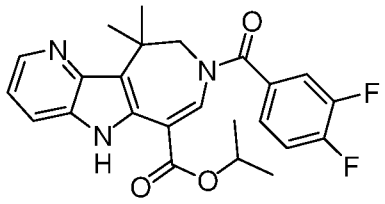


54

[00661] To a solution of compound **53** (1.0 g) in TFA (8 mL) was heated at 90°C for 2h. The TFA was removed in vacuo. The residue was dissolved in 100 mL CH_2Cl_2, washed with

saturated $NaHCO_3$, and brine. The crude mixture was purified by column chromatography to provide compound **54** (0.42 g, 76%).

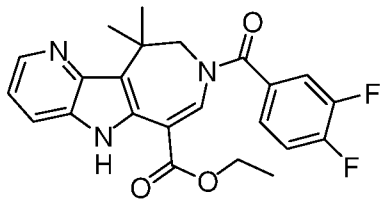
Step 12: Propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (55)



55

[00662] To a solution of compound **54** (40 mg, 1.0 eq) and DIEA (52 mg, 3.0 eq) CH_2Cl_2 (3 mL) was added 3,4-difluorobenzoyl chloride (59 mg, 2.5 eq). The resulting mixture was stirred at room temperature for 2h. The mixture was washed with saturated $NaHCO_3$ and brine. The crude mixture was purified by column chromatography to provide compound **55** (42 mg, yield 71%). LC-MS: 440.4 (M+H).

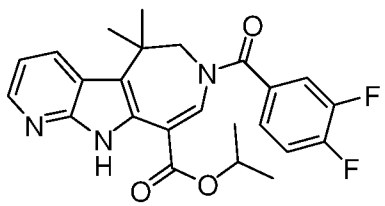
Example 9: Synthesis of eth-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (56)



56

[00663] The title compound **56** was prepared using a similar procedure as outlined in Example 8. LC-MS: 426.1 (M+H).

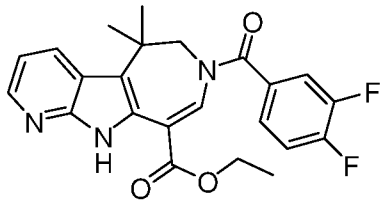
Example 10: Synthesis of propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (57)



57

[00664] The title compound **57** was prepared using a similar procedure as outlined in Example 8. LC-MS: 440.1 (M+H).

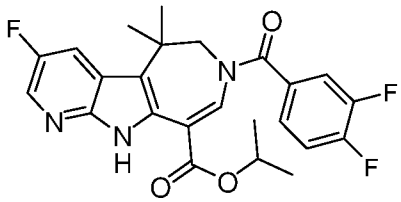
Example 11: Synthesis of eth-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (58)



58

[00665] The title compound **58** was prepared using a similar procedure as outlined in Example 8. LC-MS: 440.1 (M+H).

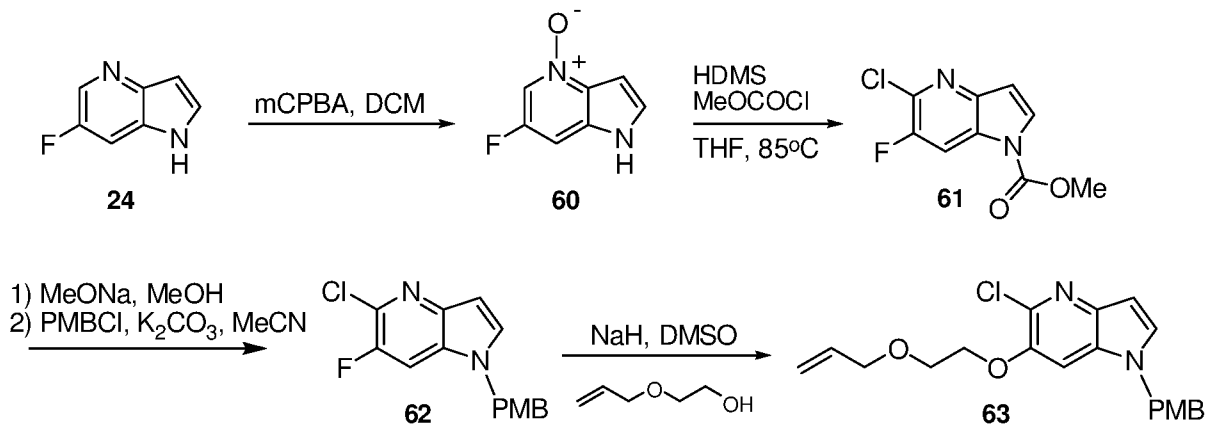
Example 12: Synthesis of propan-2-yl 4-fluoro-12-(3,4-difluorobenzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (59)

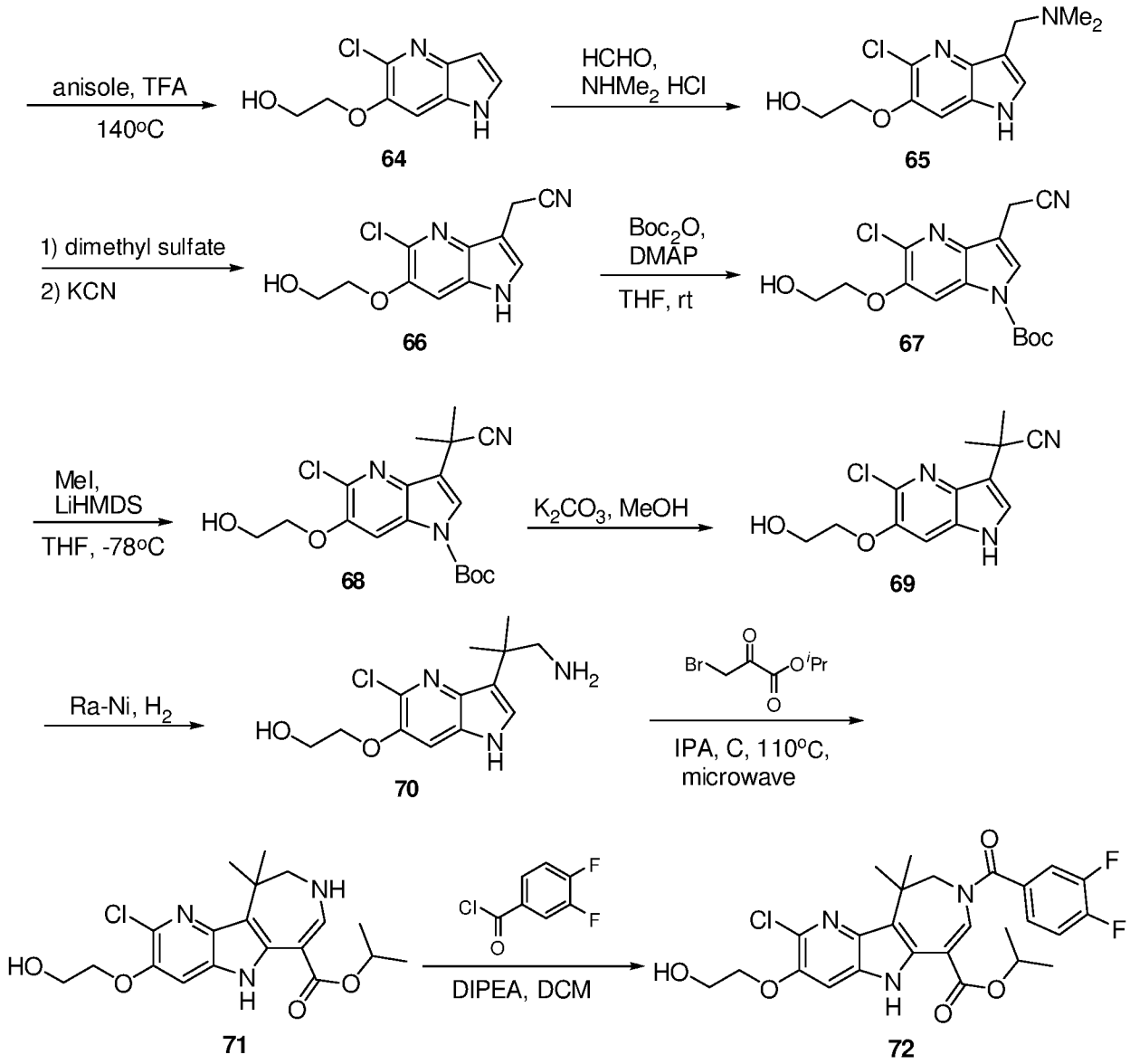


59

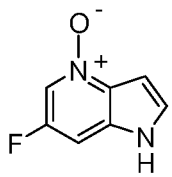
[00666] The title compound **59** was prepared using a similar procedure as outlined in Example 2. LC-MS: 440.1 (M+H).

Example 13: Synthesis of propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-5-(2-hydroxyethoxy)-4-chloro-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (72)





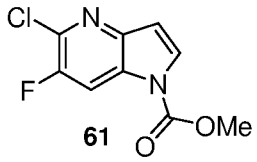
Step 1: 6-Fluoro-1H-pyrrolo[3,2-b]pyridine N-oxide (60)



60

[00667] To a stirred solution of compound **24** (1.2 g, 8.8 mol, 1.0 eq.) in DCM (100 mL), was added mCPBA (2.3 g, 13.2 mmol, 1.5 eq.) at room temperature. After stirring at room temperature overnight, the reaction was cooled at 0 °C for 1h, and then filtered to collect the solid. The solid was washed with diethyl ether, and then dried under high vacuum give compound **60** (1.3 g, 8.5 mmol, 97%) as a solid, which is used without further purification.

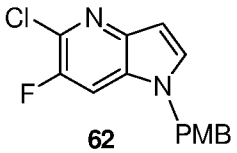
Step 2: Methyl 5-chloro-6-fluoro-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (61)



61

[00668] To a stirred suspension of compound **60** (1.3 g, 8.5 mmol, 1.0 eq.) and hexamethyldisilazane (1.5 g, 9.4 mmol, 1.1 eq.) in dry THF (80 mL), was added methyl chloroformate (2.4 g, 25.5 mmol, 3 eq.). The reaction was stirred at room temperature for 1h, and then at 85 °C for 20 hr. The reaction was quenched with ice/water, and extracted with EtOAc. The organic solution was dried over Na_2SO_4, and concentrated to give compound **61** (1.6 g, 7.0 mmol, 82%) as yellow solid, which is used without further purification.

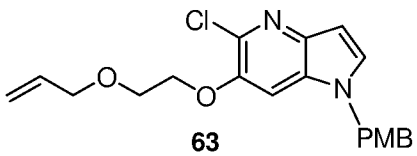
Step 3: 5-Chloro-6-fluoro-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridine (62)



62

[00669] To a stirred solution of compound **61** (1.6 g, 7.0 mmol, 1.0 eq.) in MeOH, was added MeONa (1.5 g, 21 mmol, 3 eq.) at 0 °C. After stirring at 0 °C for 15 min, MeOH was removed under vacuum. The residue was suspended in water, the pH was adjusted to neutral, and the mixture was extracted with EtOAc (2x). The organic solution was dried over Na_2SO_4 and concentrated to dryness to give 1.1 g yellow solid. The solid was added to a mixture of K_2CO_3 and PMB-Cl in MeCN (50 mL). The reaction was heated at reflux for 4h and then cooled to room temperature. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in EtOAc, and washed with water and brine. The organic phase was concentrated. The residue was purified by silica gel column chromatography to give compound **62** (1.3 g, 4.5 mmol, 65%) as a white solid.

Step 4: 6-(2-(Allyloxy)ethoxy)-5-chloro-1-(4-methoxybenzyl)-1H-pyrrolo[3,2-b]pyridine (63)

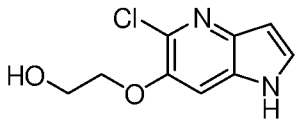


63

[00670] To a solution of 2-allyloxyethanol (0.55 g, 5.4 mmol, 1.2 eq.) in dry DMSO (10 mL), was added NaH (217 mg, 5.4 mmol, 1.2 eq.). After stirring at room temperature for 30 min, a solution of compound **62** in DMSO (1.5 mL) was dropped in. The reaction was heated to 80 °C and stirred overnight. The reaction was quenched with water, and extracted with EtOAc/hexane (8/2). The organic phase was washed with water, dried over Na_2SO_4, and concentrated. The

residue was purified by silica gel column chromatography to give compound **63** (1.4 g, 3.7 mmol, 83%) as a white solid.

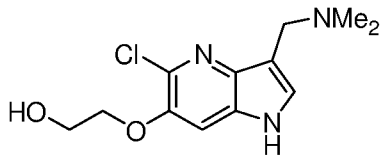
Step 5: 2-(5-Chloro-1H-pyrrolo[3,2-b]pyridin-6-yloxy)ethanol (64)



64

[00671] A mixture of compound **63** (1.4 g, 3.7 mmol, 1.0 eq.) and anisole (1.14 g, 11.1 mmol, 3 eq.) in 20 mL TFA was stirred at 130 °C for 48 hrs. The TFA was removed under high vacuum. The residue was dissolved in DCM, and washed carefully with saturated $NaHCO_3$ solution twice. The organic solution was dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography to give compound **64** (630 mg, 3.0 mmol, 77%) as a yellow solid.

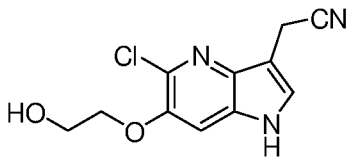
Step 6: 2-(5-Chloro-3-((dimethylamino)methyl)-1H-pyrrolo[3,2-b]pyridin-6-yloxy)ethanol (65)



65

[00672] To a stirred solution of compound **64** (630 mg, 2.97 mmol, 1.0 eq.) in n-BuOH (10 mL), was added 37 % formaldehyde in water (2.6 mL, 3.3 mmol, 1.1 eq.) and dimethylamine hydrochloride (280 mg, 3.4 mmol, 1.15 eq.). The reaction mixture was heated at reflux for 3h. After cooling down, the reaction was poured into 1N HCl (80 mL). The butanol layer was discarded and the water phase was adjusted to pH 13-14 with 2M NaOH. The resulting mixture was extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated to give compound **65** (490 mg, 61%), which was used in the next reaction without purification.

Step 7: 2-(5-Chloro-6-(2-hydroxyethoxy)-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (66)

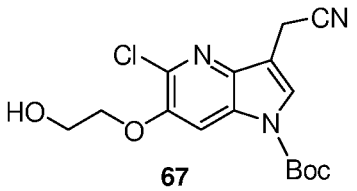


66

[00673] To a stirred solution of compound **65** (490 mg, 1.83 mmol, 1.0 eq.) in dry THF (15 mL), was added dimethyl sulfate (253 mg, 2.0 mmol, 1.1 eq.) dropwise at 0 °C. The mixture was heated at reflux for 1h and cooled down. The solvent was decanted and the glue like precipitate was collected and washed with hexane. The residue was dissolved in 20 mL water and KCN

(155 mg, 2.38 mmol, 1.3 eq.) was added. The reaction was heated at reflux for 1.5h, then allowed to cool. The reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic phase was dried over Na_2SO_4, and concentrated to give compound **66** (460 mg, 99%), which was used in the next reaction without purification.

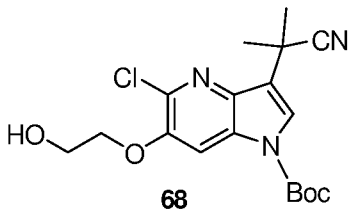
Step 8: tert-Butyl 5-chloro-3-(cyanomethyl)-6-(2-hydroxyethoxy)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (67)



67

[00674] To a stirred solution of compound **66** (460 mg, 1.8 mmol, 1.0 eq.) and DMAP (22 mg, 0.18 mmol, 0.1 eq.) in dry THF (15 mL), was added Boc_2O (864 mg, 4.0 mmol, 2.2 eq.). The mixture was stirred at room temperature for 30 min, and then diluted with EtOAc (40 mL). The mixture was washed with 1N HCl, saturate $NaHCO_3$, and water. The organic phase was dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography to give compound **67** (380 mg, 47%) as a white solid.

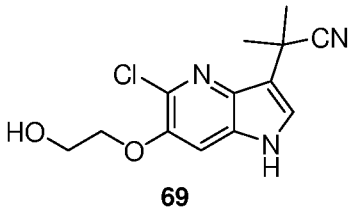
Step 9: tert-butyl 5-chloro-3-(2-cyanopropan-2-yl)-6-(2-hydroxyethoxy)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (68)



68

[00675] To a stirred solution of compound **67** (380 mg, 0.84 mmol, 1.0 eq.) and iodomethane (360 mg, 2.5 mmol, 3 eq.) in dry THF (5 mL), was added 1M LiHMDS in THF (2.5 mL, 3 eq.) dropwise at -78 °C. After stirring at -78 °C for 30 min, the reaction was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography to give compound **68** (250 mg, 63 %) as a white solid.

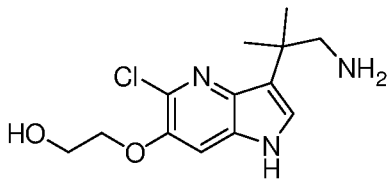
Step 10: 2-(5-Chloro-6-(2-hydroxyethoxy)-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (69)



69

[00676] To a stirred solution of compound **68** (250 mg, 0.52 mmol, 1.0 eq.) in MeOH (5 mL), was added K_2CO_3 (215 mg, 1.56 mmol, 3 eq.). After stirring at 60 °C for 2h, the reaction was allowed to cool down, and the solid was filtered off. The solution was concentrated. The residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4. The solution was concentrated to dryness to give compound **69** (150 mg, 100 %) as a white solid.

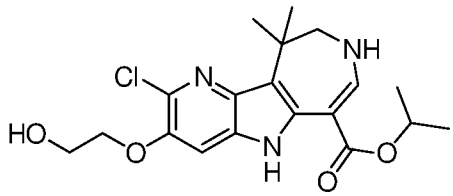
Step 11: 2-(3-(1-Amino-2-methylpropan-2-yl)-5-chloro-1H-pyrrolo[3,2-b]pyridin-6-yloxy)ethanol (70)



70

[00677] To solution of compound **69** (150 mg, 0.52 mmol, 1 eq.) with raney nickel (0.1 g in water) was hydrogenated in Parr hydrogenator (60 psi) at room temperature overnight. The solid was filtered off and the filtrate was concentrated to afford compound **70** (110 mg, 75 %), which was used in the next reaction without purification.

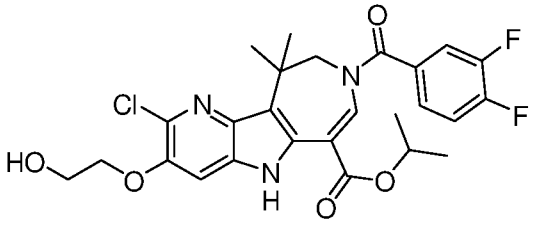
Step 12: Isopropyl 3-(2-hydroxyethoxy)-2-chloro-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (71)



71

[00678] A mixture of compound **70** (110 mg, 0.39 mmol, 1.0 eq.), isopropyl 3-bromo-2-oxopropanoate (97 mg, 0.47 mmol, 1.2 eq.), and activated carbon (3 mg) in isopropanol (3 mL) was stirred at 110 °C for 2h under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. The residue was purified with silica gel column chromatography to give compound **71** (22.5 mg, 15 %) as a white solid.

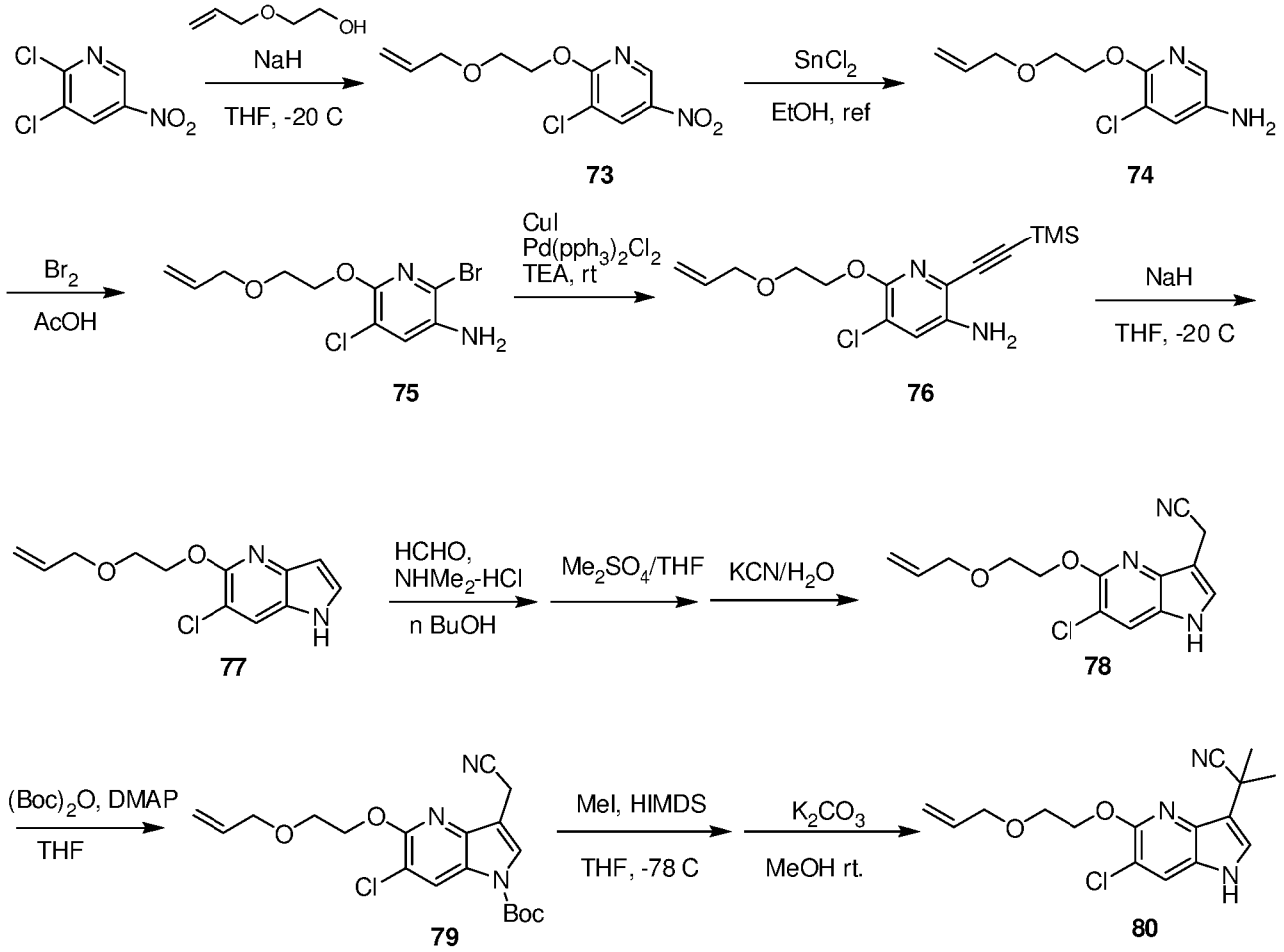
Step 13: Propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-5-(2-hydroxyethoxy)-4-chloro-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (72)

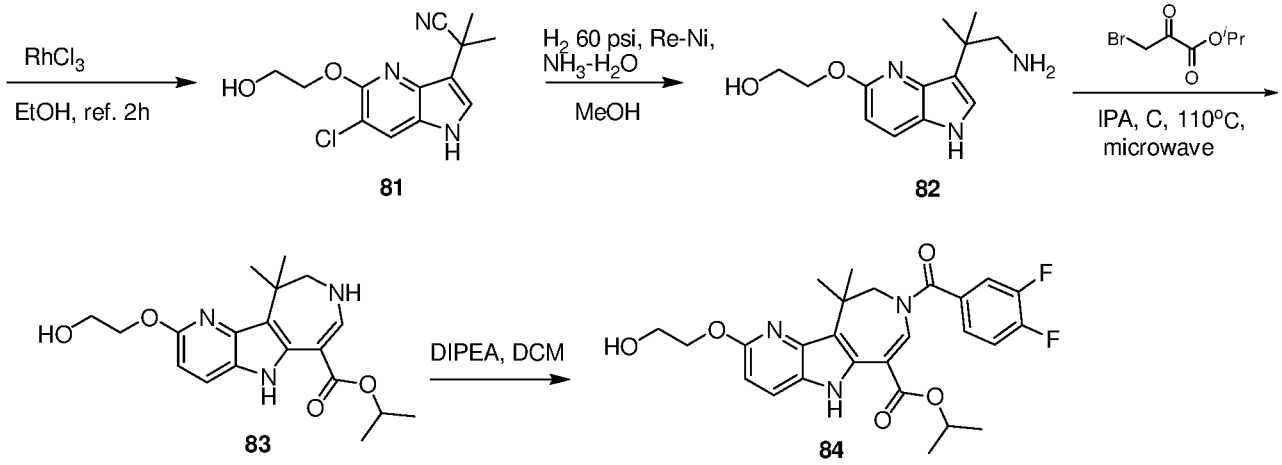


72

[00679] To a solution of compound **71** (22.5 mg, 0.06 mmol, 1.0 eq.) and DIPEA (15 mg, 0.12 mmol, 2 eq.) in dichloromethane (2 mL), was added 3,4-difluorobenzoyl chloride (12.3 mg, 0.07 mmol, 1.1 eq.) in DCM (1 mL). The reaction mixture was stirred for 30 min at room temperature, then washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to give compound **72** (20 mg, 64 %) as a yellow solid. LC-MS: 534.4 (M+H).

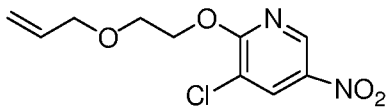
Example 14: Synthesis of propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-4-(2-hydroxyethoxy)-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (84)





81 82 83 84

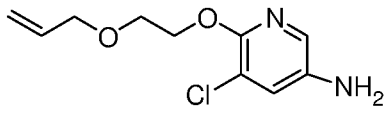
Step 1: 2-(2-(Allyloxy)ethoxy)-3-chloro-5-nitropyridine (73)



73

[00680] To a solution of 2-allyloxyethanol (5.8 g, 57 mmol, 1.1 eq.) in dry THF (10 mL), was added NaH (1.37 g, 57 mmol, 1.1 eq.). After stirring at room temperature for 30 min, the solution was dropped into a solution of 2, 3-dichloro-5-nitropyridine (10 g, 52 mmol, 1 eq.) in THF (10 mL) at -20 °C. The reaction was stirred for 1 hr. at room temperature, quenched with water (50 mL), and extracted with EtOAc. The organic phase was washed with water, dried over Na_2SO_4, and concentrated to give compound **73** (13 g, 97%) as a brown oil.

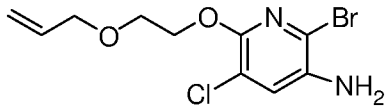
Step 2: 6-(2-(Allyloxy)ethoxy)-5-chloropyridin-3-amine (74)



74

[00681] To a solution of $SnCl_2$-$2H_2O$ (6 g, 26 mmol, 2 eq.) in EtOH (40 mL) was added compound **73** (3.5 g, 13.5 mmol, 1.0 eq.). The reaction was heated to reflux. $SnCl_2$-$2H_2O$ (3 g, 13 mmol, 1 eq.) was added to the reaction every 30 min until a total 5 eq. of $SnCl_2$-$2H_2O$ was added. After heating at reflux overnight, the solvent was removed under vacuum. Water was added to the residue. The pH was adjusted to 13-14 with 4N NaOH solution, and the mixture was extracted with EtOAc. The organic phase was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc) to give compound **74** (750 mg, 24 %) as a yellow oil.

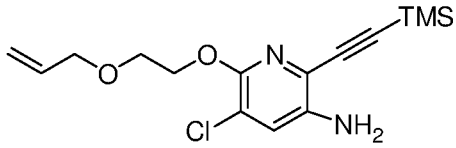
Step 3: 6-(2-(Allyloxy)ethoxy)-2-bromo-5-chloropyridin-3-amine (75)



75

[00682] To a solution of compound **74** (750 mg, 3.2 mmol, 1 eq.) in acetic acid (10 mL), was added bromine (1.0 g, 6.4 mmol, 2 eq.). The mixture was stirred at 100 °C for 6 h. Excess Br_2 and AcOH was removed under high vacuum to give compound **75** (780 mg, 77 %).

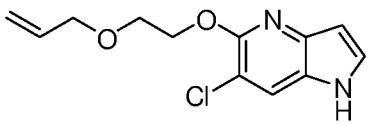
Step 4: 6-(2-(Allyloxy)ethoxy)-5-chloro-2-((trimethylsilyl)ethynyl)pyridin-3-amine (76)



76

[00683] To a stirred mixture of compound **75** (780 mg, 2.5 mmol, 1 eq.), $Pd(PPh_3)_2Cl_2$ (183 mg, 0.26 mmol, 0.1 eq.), and CuI (50 mg, 0.26 mmol, 0.1 eq.) in trimethylamine (20 ml), was added ethynyltrimethylsilane (301 mg, 3.1 mmol, 1.2 eq.) at 0 °C. The reaction was stirred for 3 hr at room temperature under nitrogen. LCMS indicated the starting material has been consumed and two new products were formed. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/DCM) to give compound **76** (620 mg, 77 %) as a yellow oil.

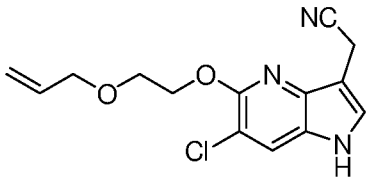
Step 5: 5-(2-(Allyloxy)ethoxy)-6-chloro-1H-pyrrolo[3,2-b]pyridine (77)



77

[00684] To a solution of compound **76** (620 mg, 1.9 mol, 1.0 eq.) in dry DMF (20 mL), was added NaH (185 mg, 7.6 mmol, 4 eq.) at 0 °C. After stirring at room temperature for 5 hr, the reaction was poured into 50 mL ice/water, and extracted with EtOAc/hexane (9/1, 40 mL X 2). The organic phase was washed with water, brine, dried with Na_2SO_4, and concentrated to dryness. The residue was purified with silica gel column chromatography (hexane/EtOAc) to give compound **77** (210 mg, 44%) as a brown solid.

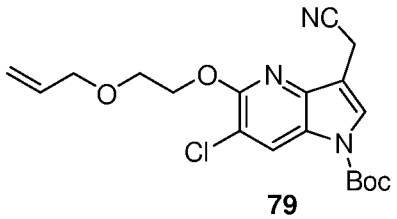
Step 6: 2-(5-(2-(Allyloxy)ethoxy)-6-chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetonitrile (78)



78

[00685] To a solution of compound **77** (210 mg, 0.83 mmol, 1.0 eq.) in n-BuOH (4 mL), was added 37 % formaldehyde in water (0.8 mL, 1 mmol, 1.2 eq.) and dimethylamine hydrochloride (82 mg, 1 mmol, 1.2 eq.). The reaction was heated at reflux for 1h. After cooling down, the reaction was poured into 1N HCl (80 mL). The butanol layer was discarded and the water phase was adjusted to pH 13-14 with 2M NaOH. The resulting mixture was extracted with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (6 mL), and dimethyl sulfate (126 mg, 1 mmol, 1.2 eq.) was added dropwise at 0 °C. The mixture was heated at reflux for 1h and concentrated. The residue was dissolved in H_2O/THF (5/1, 12 mL) and KCN (82 mg, 1.25 mmol, 1.5 eq.) was added. The reaction was heated at reflux for 1h, then allowed to cool down. The reaction was extracted with EtOAc (20 mL X 3). The combined organic phase was dried over Na_2SO_4, and concentrated to give compound **78** (270 mg), which was used in the next reaction without purification.

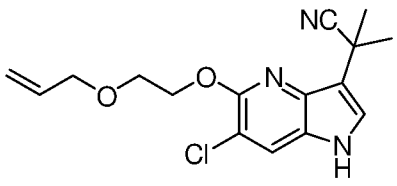
Step 7: tert-Butyl 5-(2-(allyloxy)ethoxy)-6-chloro-3-(cyanomethyl)-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (79)



79

[00686] To a solution of compound **78** (270 mg, 0.93 mmol, 1.0 eq.) and DMAP (11 mg, 0.09 mmol, 0.1 eq.) in dry THF (5 mL), was added Boc_2O (222 mg, 1.0 mmol, 1.1 eq.). The mixture was stirred at room temperature for 1.5 hr., and then diluted with EtOAc (20 mL). The mixture was washed with 1N HCl, saturate $NaHCO_3$, and water. The organic phase was dried over Na_2SO_4, and concentrated to give compound **79** (390 mg), which was used in the next reaction without purification.

Step 8: 2-(5-(2-(Allyloxy)ethoxy)-6-chloro-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (80)

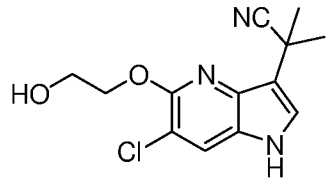


80

[00687] To a solution of compound **79** (390 mg, 0.99 mmol, 1.0 eq.) and iodomethane (355 mg, 2.5 mmol, 2.5 eq.) in dry THF (4 mL), was added 1M LiHMDS in THF (2.5 mL, 2.5 eq.) dropwise at -78 °C. After stirring at -78 °C for 30 min, the reaction was quenched with water, and extracted with EtOAc. The organic phase was washed with water and brine, dried over

Na_2SO_4, and concentrated. The residue and K_2CO_3 (420 mg, 3 mmol, 3 eq.) was dissolved in MeOH (5 mL). After stirring at room temperature for 30 min, the solid was filtered out and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography (hexane/EtOAc) to give compound **80** (150 mg, 56% from compound **77**) as a white solid.

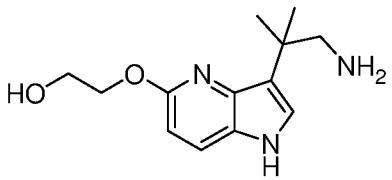
Step 9: 2-(6-Chloro-5-(2-hydroxyethoxy)-1H-pyrrolo[3,2-b]pyridin-3-yl)-2-methylpropanenitrile (81)



81

[00688] To a solution of $RhCl_3$-H_2O (30 mg, 0.14 mmol, 0.3 eq.) in EtOH (5 mL), was added compound **80** (150 mg, 0.47 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 2h. and concentrated. The residue was purified with silica gel column chromatography (DCM/THF) to give compound **81** (110 mg, 84%) as a yellow oil.

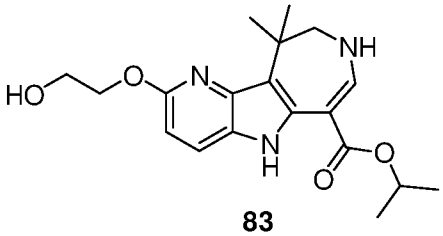
Step 10: 2-(3-(1-Amino-2-methylpropan-2-yl)-1H-pyrrolo[3,2-b]pyridin-5-yloxy)ethanol (82)



82

[00689] A solution of compound **81** (110 mg, 0.39 mmol, 1 eq.) with raney nickel (0.1 g in water) was hydrogenated in Parr hydrogenator (60 psi) at room temperature overnight. The solid was filtered off and the filtrate was concentrated to afford compound **82** (90 mg, 92% yield), which was used in the next reaction without purification.

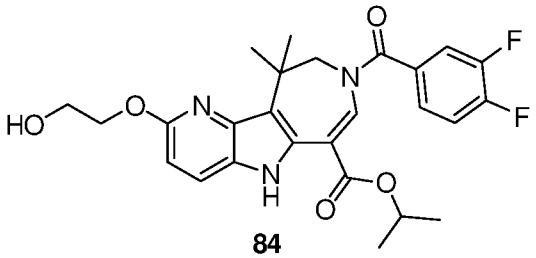
Step 11: Isopropyl 2-(2-hydroxyethoxy)-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxylate (83)



83

[00690] A mixture of compound **82** (90 mg, 0.36 mmol, 1.0 eq.), isopropyl 3-bromo-2-oxopropanoate (85 mg, 0.4 mmol, 1.1 eq.), and activated carbon (3 mg) in isopropanol (3 mL) was stirred at 110 °C for 1h under microwave irradiation. Activated carbon was filtered off and the filtrate was concentrated. The residue was purified with silica gel column chromatography to give compound **83** (44 mg, 34%) as a yellow solid.

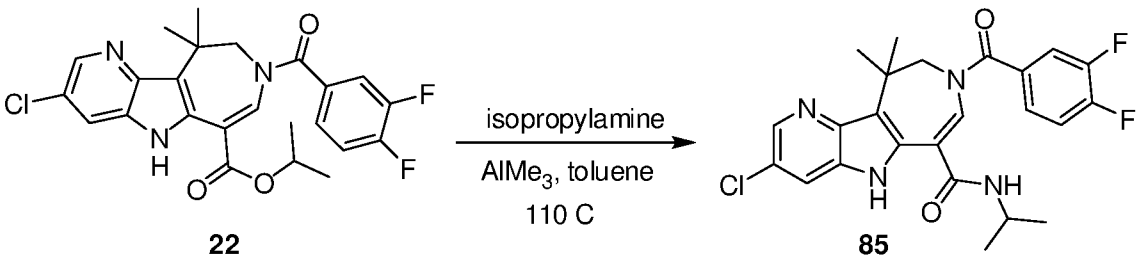
Step 12: Propan-2-yl 12-(3,4-difluorobenzoyl)-14,14-dimethyl-4-(2-hydroxyethoxy)-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (84)



84

[00691] To a solution of compound **83** (44 mg, 0.12 mmol, 1.0 eq.) and DIPEA (24 mg, 0.18 mmol, 1.5 eq.) in dichloromethane (4 mL), 3,4-difluorobenzoyl chloride (19.4 mg, 0.11 mmol, 0.9 eq.) in DCM (1 mL) was added. The reaction mixture was stirred for 30 min at room temperature, then washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, and concentrated. The residue was purified with silica gel column chromatography (DCM/EtOAc) to give compound **84** (30 mg, 50 %) as a yellow solid. LC-MS: 500.5 (M+H).

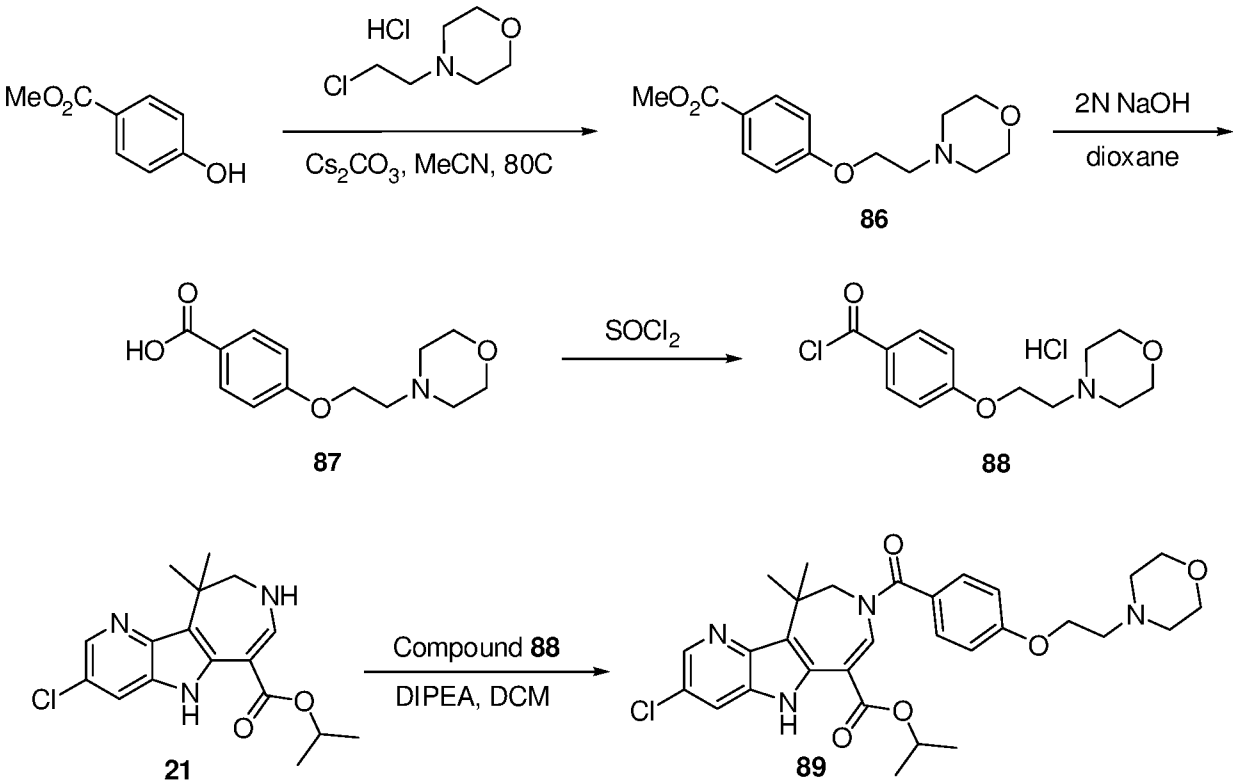
Example 15: Synthesis of 3-chloro-8-(3,4-difluorobenzoyl)-N-isopropyl-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxamide (85)



22 85

[00692] To a solution of isopropyl amine (70 mg, 1.10 mol) in toluene, trimethyl aluminium [0.4 mL (2 M solution in toluene), 0.90 mol] was added at 0°C. After 15 minutes, compound **22** (110 mg, 0.23 mol) was added and reaction mixture was heated at 110°C in a seal tube for 16 h. The reaction was quenched with ice water and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel using 30% ethyl acetate in hexane to afford compound **85** (40 mg, 51%) as a yellow solid. LC-MS: 473.1.

Example 16: Synthesis of propan-2-yl 4-chloro-12-(4-(2-morpholinoethoxy)benzoyl)-14,14-dimethyl-6,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (89)



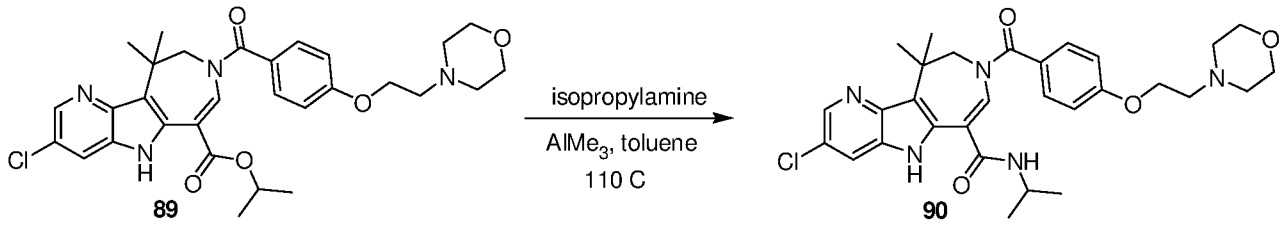
[00693] To a solution of methyl 4-hydroxybenzoate (68.1 g, 1.0 eq.) in acetonitrile (1.3 L) was added N-(2-chloroethyl) morpholine HCl salt (99.9 g, 1.2 eq.) and Cs_2CO_3 (291.7 g, 2.0 eq.). The resulting mixture was stirred and heated at reflux (80°C oil bath) overnight. The reaction mixture was cooled to room temperature and the inorganic solid was filtered off. The solvent was evaporated. The oily residue was dissolved in EtOAc/hexane mixture (3:1, 500 mL) and washed with water (500 mL). The aqueous layer was re-extracted more with EtOAc/hexane (3:1, 2 x 100 mL). The combined organic extracts were evaporated in vacuo to give compound **86** (126.1 g) as pale-yellow oil which was used without purification.

[00694] A suspension of compound **86** (126.1 g) in 6N HCl (880 mL) was heated at reflux (oil bath at 135°C) overnight. The reaction mixture was concentrated in vacuo to remove most water then cooled at 0°C. The resulted precipitate was filtered, washed with cold 2N HCl (2 x 100 mL) to give a white solid. The solid was dried in high vacuum to give compound **87** HCl salt (112.9 g, 82%).

[00695] A suspension of compound **87** HCl salt (112.8 g) in $SOCl_2$ (450 mL) was heated at 90°C for 12h. The excess $SOCl_2$ was removed in vacuo to ~225 mL and the product was precipitated with heptane (560 mL) to provide a white solid. The solid was filtered, washed with heptane and dried on high vacuo to afford compound **88** HCl salt (116 g, 98%).

[00696] Compound **89** was prepared from compound **21** and compound **88** using conditions as described in Example 4, step 11. LC-MS: 567.

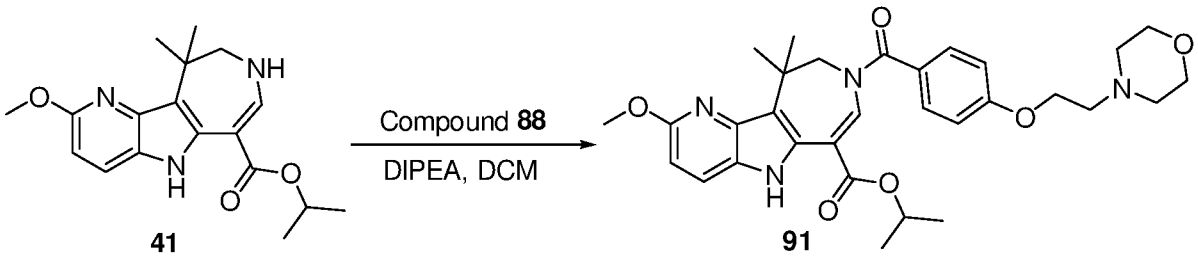
Example 17: Synthesis of 3-chloro-8-(4-(2-morpholinoethoxy)benzoyl)-N-isopropyl-10,10-dimethyl-5,8,9,10-tetrahydropyrido[2',3':4,5]pyrrolo[2,3-d]azepine-6-carboxamide (90)



89 90

[00697] Compound **90** was prepared from compound **89** using conditions as described in Example 15. LC-MS: 566.4.

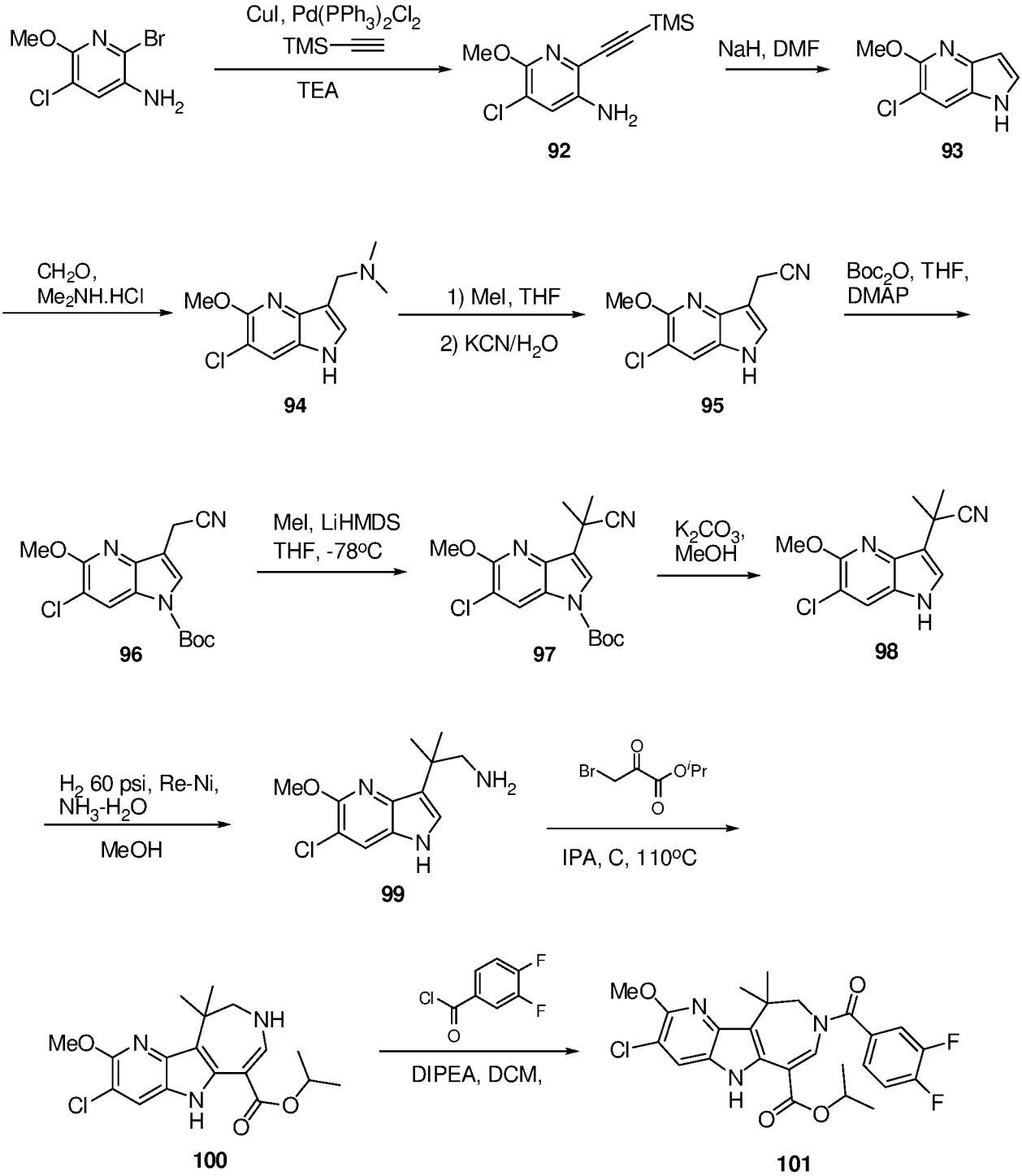
Example 18: Synthesis of propan-2-yl 12-(4-(2-morpholinoethoxy)benzoyl)-14,14-dimethyl-4-(methoxy)-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (91)



41 91

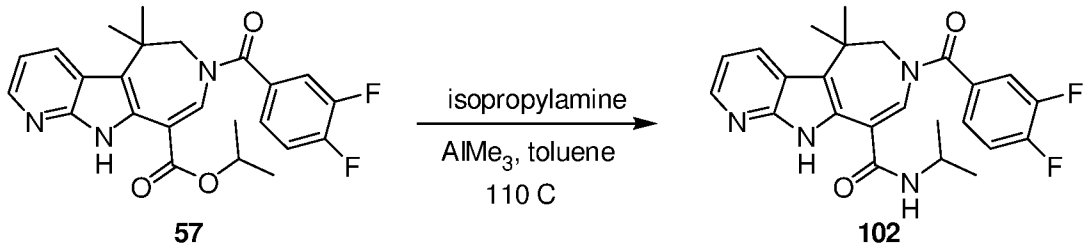
[00698] Compound **91** was prepared from compound **41** and compound **88** using conditions as described in Example 6, step 9. LC-MS: 563.5 (M+H).

Example 19: Synthesis of propan-2-yl 5-chloro-4-methoxy-12-(3,4-difluorobenzoyl)-14,14-dimethyl-3,8,12-triazatricyclo[7.5.0.02,7]tetradeca-1(9),2,4,6,10-pentaene-10-carboxylate (101)



[00699] Compound **101** was prepared using conditions outlined above and as described in Example 4. LC-MS: 504.4 (M+H).

Example 20: Synthesis of 12-(3,4-difluorobenzoyl)-14,14-dimethyl-N-(propan-2-yl)-6,8,12-triazatricyclo[7.5.0.0^{2,7}]tetradeca-1(9),2,4,6,10-pentaene-10-carboxamide (102)



57 102

[00700] Compound **102** is prepared from compound **57** using conditions described in Example 15.

Example 21: FXR Agonist Transactivation Assay

[00701] For the transactivation assay, cells were transiently transfected with 100 ng of reporter vector and 10 ng of expression plasmid. Forty nanograms of pGL4.74 was used as internal control for transfection efficiency. The pGEM vector was added to normalize the amounts of DNA transfected in each assay (2 μg). All transfections were performed using FuGENE HD (Roche, Mannheim, Germany) according to the manufacturer's protocol. Twenty-four hours after transfection, cells were stimulated with increasing concentrations of the test compounds for further 18 h. Control cultures receive vehicle (0.1% DMSO) alone. Luciferase values were normalized with *Renilla reniformis* luciferase units, for transfection efficiency. Data are shown below in Table 1.

Table 1

Compound	EC50 (μM)
9	B
10	A
11	B
22	A
33	A
42	A
43	A
55	A
56	A
57	A
58	A
59	A
72	B
84	A
85	A
89	A
90	NT
91	A
101	A

A, EC_{50} < 1 μM; B, EC_{50} = 1-10 μM; NT=not tested

Example 22: Phase 1 Study to Evaluate Safety of a Compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) in Subjects With Non-Alcoholic Steatohepatitis (NASH) and Advanced Fibrosis

[00702] The primary objective of this study is to characterize the safety, tolerability and dose-limiting toxicities (DLTs) for a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) when administered orally to subjects with biopsy-proven NASH with advanced liver fibrosis.

- The safety and tolerability of multiple doses of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV);
- The effects of 2 dose levels (25 mg and 50 mg) of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) on insulin resistance and glucose homeostasis; and
- Effects of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) on hepatocellular function as measured by assessment of liver enzymes and biochemical markers of hepatic and metabolic function and inflammation.

[00703] Patients: Eligible subjects will be men and women 18 years to 75 years of age.

[00704] Criteria:

Inclusion Criteria:

- Institutional Review Board (IRB approved written Informed Consent and privacy language as per national regulation (eg, Health Insurance Portability and Accountability Act [HIPAA] Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study related procedures, including screening evaluations and tests
- Subject is $\geq$ 18 years of age and < 76 years old at the time of consent
- Subject has had a percutaneous liver biopsy within 12 months from Screening that shows a definitive diagnosis of NASH with advanced (Brunt stage 3) hepatic fibrosis

Exclusion Criteria:

- Subject is a pregnant or lactating female
- Subject with current, significant alcohol consumption or a history of significant alcohol consumption for a period of more than 3 consecutive months any time within 1 year prior to screening. Significant alcohol consumption is defined as more than 20 gram per day in

females and more than 30 grams per day in males, on average (a standard drink in the US is considered to be 14 grams of alcohol).

- Subject is unable to reliably quantify alcohol consumption based upon local study physician judgment.
- Subject uses drugs historically associated with nonalcoholic fatty liver disease (NAFLD) (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins) for more than 2 weeks in the year prior to Screening.
- Subject requires use of drugs with a narrow therapeutic window metabolized by CYP3A4 such as fast acting opioids (alfentanil and fentanyl), immunosuppressive drugs (cyclosporine, sirolimus, and tacrolimus), some cardiovascular agents (ergotamine, quinidine and dihydroergotamine), and select psychotropic agents (pimozide).
- Subject has prior or has planned (during the study period) bariatric surgery (eg, gastroplasty, Roux-en-Y gastric bypass).
- Subject has concurrent infection including diagnoses of fever of unknown origin and evidence of possible central line sepsis (subjects must be afebrile at the start of therapy).
- Subject with a platelet count below 100,000/mm3 at Screening.
- Subject with clinical evidence of hepatic decompensation as defined by the presence of any of the following abnormalities at Screening:
- Serum albumin less than 3.5 grams/deciliter (g/dL).
- An INR greater than 1.1.
- Direct bilirubin greater than 1.3 milligrams per deciliter (mg/dL).
- Subject has a history of bleeding esophageal varices, ascites or hepatic encephalopathy
- Subject has a history of hepatitis C. Patients found on screening to have hepatitis C antibody, even if PCR negative for HCV RNA, are excluded from this study.
- Subject has evidence of other forms of chronic liver disease:
- Hepatitis B as defined by presence of hepatitis B surface antigen.
- Evidence of ongoing autoimmune liver disease as defined by compatible liver histology.
- Primary biliary cirrhosis as defined by the presence of at least 2 of these criteria (i) Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation (ii) Presence of anti-mitochondrial antibody (iii) Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts.
- Primary sclerosing cholangitis.

- Wilson's disease as defined by ceruloplasmin below the limits of normal and compatible liver histology.
- Alpha-1-antitrypsin deficiency as defined by diagnostic features in liver histology (confirmed by alpha-1 antitrypsin level less than normal; exclusion at the discretion of the study physician).
- History of hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy.
- Drug-induced liver disease as defined on the basis of typical exposure and history.
- Known bile duct obstruction.
- Suspected or proven liver cancer.
- Any other type of liver disease other than NASH.
- Subject with serum ALT greater than 300 units per liter (U/L) at Screening.
- Subject with serum creatinine of 1.5 mg/dL or greater at Screening.
- Subject using of any prescription or over-the-counter medication or herbal remedy that are believed to improve or treat NASH or liver disease or obesity during the period beginning 30 days prior to randomization. Subjects who are using Vitamin E or omega-3 fatty acids may continue their use.
- Subject had major surgery within 8 weeks prior to Day 0, significant traumatic injury, or anticipation of need for major surgical procedure during the course of the study.
- Subject with a history of biliary diversion.
- Subject with known positivity for Human Immunodeficiency Virus infection.
- Subject with an active, serious medical disease with likely life expectancy of less than 5 years.
- Subject with active substance abuse, including inhaled or injection drugs, in the year prior to Screening.
- Subject who has clinically significant and uncontrolled cardiovascular disease (eg, uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or Grade II or greater peripheral vascular disease within 12 months prior to Day 0.
- Subject has participated in an investigational new drug (IND) trial in the 30 days before randomization.
- Subject has a clinically significant medical or psychiatric condition considered a high risk for participation in an investigational study.

- Subject has any other condition which, in the opinion of the Investigator, would impede compliance or hinder completion of the study.
- Subject has been previously exposed to GR MD 02.
- Subject with known allergies to the study drug or any of its excipients.
- Subject with malignant disease (other than basal and squamous cell carcinoma of the skin and in situ carcinoma of the cervix) with at least 5 years of follow-up showing no recurrence.
- Subject has an abnormal chest x-ray indicative of acute or chronic lung disease on screening examination.

[00705] Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

[00706] Primary Outcome Measures:

The primary objective of this study is to characterize the safety, which includes the tolerability and dose-limiting toxicity (DLT), for a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) when administered intravenously to subjects with biopsy-proven NASH with advanced liver fibrosis. Specifically, this measure will be assessed by number of subjects experiencing treatment emergent adverse events indicative of DLT.

[00707] Secondary Outcome Measures:

- A secondary objective is to characterize the first-dose PK profile of compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV). The PK profile is assessed by the AUC (area under the plasma concentration versus time curve) and Cmax (peak plasma concentration) of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV).
- A secondary objective for the study is to characterize the PK profile and serum level accumulation of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) following administration of daily oral doses beginning 3 days after the first dose.
- A secondary objective is to evaluate change in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), ratio of AST:ALT, alkaline phosphatase, and gamma

glutamyl transpeptidase (GGTP); change in AST/platelet ratio index. [Time Frame: Baseline; Week 7 (End of Study)] [Designated as safety issue: No]

- A secondary objective for this study is to evaluate change in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), ratio of AST:ALT, alkaline phosphatase, and gamma glutamyl transpeptidase (GGTP) levels; and change in AST/platelet ratio index.
- A secondary objective for this study is to evaluate changes in exploratory pharmacodynamic biomarkers in serum [Time Frame: Baseline; Week 7 (End of Study)] [Designated as safety issue: No]
- A secondary objective for this study is to evaluate levels of exploratory pharmacodynamic biomarkers in serum including galectin-3, inflammatory, cell-death, and fibrosis markers
- Hepatocellular function as measured by assessment of liver enzymes and biochemical markers of hepatic and metabolic function.

Arms	Assigned Interventions
Active Comparator: Cohort 1 Patient receives dose of compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) or placebo	Drug: Compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) Drug: Placebo
Active Comparator: Cohort 2 Patient receives dose of compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) or Placebo	Drug: Compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) Drug: Placebo
Active Comparator: Cohort 3 Patient receives dose of compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa),	Drug: Compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) Drug: Placebo

(IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) or placebo	

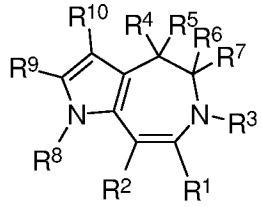
[00708] This study is a dose ranging study to assess in sequential fashion, the safety, tolerability, and dose limiting toxicities (DLTs) of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV), in subjects with biopsy-proven NASH with advanced fibrosis. This is a dose escalation design comprised of 3 sequential cohorts to evaluate the safety of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) when administered orally once a day for 7 weeks. Each cohort will consist of 8 subjects, 6 randomized to receive a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (III), or (IV) and 2 randomized to receive placebo. Based on data safety monitoring board (DSMB) and FDA review, 2 additional cohorts may be implemented, consisting of 8 subjects.

[00709] The examples and embodiments described herein are for illustrative purposes only and in some embodiments, various modifications or changes are to be included within the purview of disclosure and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

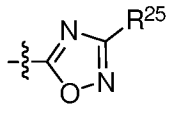
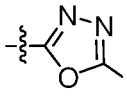
1. A compound having the Formula (I), or a pharmaceutically acceptable salt, solvate, or prodrug thereof:



Formula (I);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^3 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, optionally substituted -(C_1-C_2alkylene)-(heteroaryl), -C(O)R^{20}, -C(O)OR^{20}, -S(O)$_2R^{20}$, -C(O)N(R^{21})R^{22}, -C(O)N(R^{21})S(O)$_2R^{24}$, -C(O)N(R^{23})N(R^{21})R^{22}, -C(O)N(R^{23})N(R^{21})S(O)$_2R^{24}$, -N(R^{23})C(O)R^{20}, -N(R^{23})C(O)N(R^{21})R^{22}, -N(R^{23})C(O)N(R^{21})S(O)$_2R^{24}$, -N(R^{20})C(O)N(R^{23})N(R^{21})R^{22}, -N(R^{20})C(O)N(R^{23})N(R^{21})S(O)$_2R^{24}$, -N(R^{23})C(O)OR^{20}, -P(O)OR^{20}, and -P(O)(OR^{19})OR^{20};

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted

C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{19}, R^{20}, and R^{23} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{21} and R^{22} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

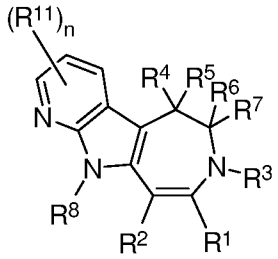
R^{24} is selected from the group consisting of optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted, aryl optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); and

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl,

optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ia):



Formula (Ia);

wherein:

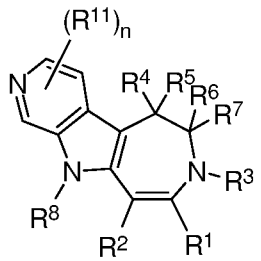
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ib):



Formula (Ib);

wherein:

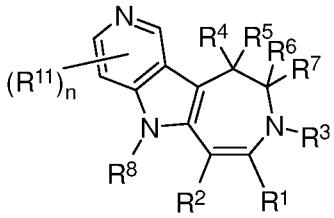
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ic):



Formula (Ic);

wherein:

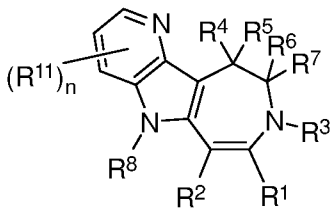
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Id):



Formula (Id);

wherein:

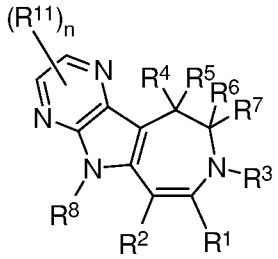
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

6. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ie):



Formula (Ie);

wherein:

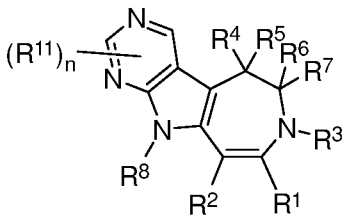
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

7. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (If):



Formula (If);

wherein:

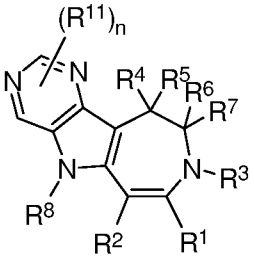
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

8. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ig):



Formula (Ig);

wherein:

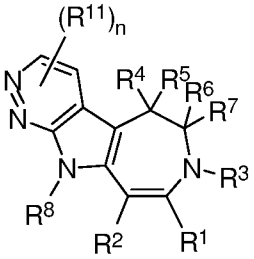
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

9. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ih):



Formula (Ih);

wherein:

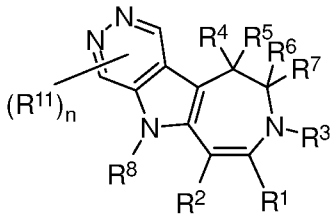
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

10. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ii):



Formula (Ii);

wherein:

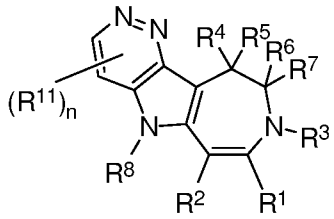
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

11. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (Ij):



Formula (Ij);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

12. The compound of any one of claims 2-11, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^6 and R^7 are hydrogen.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl.

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are methyl.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is -C(O)N(R^{21})R^{22}.

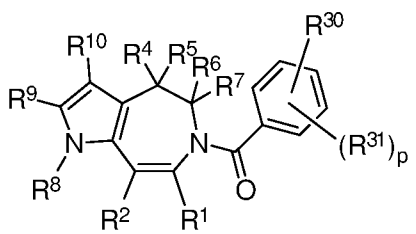
17. The compound of claim 16, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{21} is hydrogen and R^{22} is optionally substituted aryl.

18. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is -C(O)R^{20}.

19. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^3 is -S(O)$_2$$R^{20}$.

20. The compound of claim 18 or 19, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{20} is optionally substituted aryl.

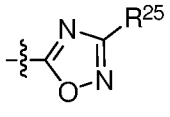
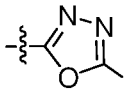
21. A compound having the structure of Formula (II), or a pharmaceutically acceptable salt, solvate, or prodrug thereof:



Formula (II);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

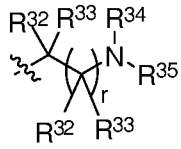
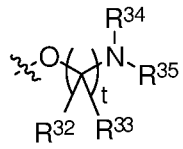
R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^9 and R^{10} together with the carbon atoms to which they are attached, form an optionally substituted nitrogen containing 6-membered heteroaryl ring;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen,  , or  ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

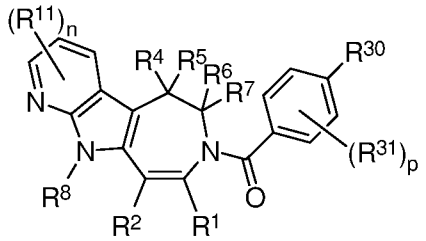
R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

22. The compound of claim 21, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIa):



Formula (IIa);

wherein:

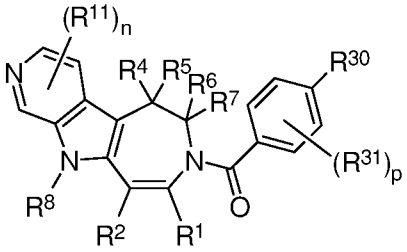
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)$N(R^{13})R^{14}$;

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

23. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIb):



Formula (IIb);

wherein:

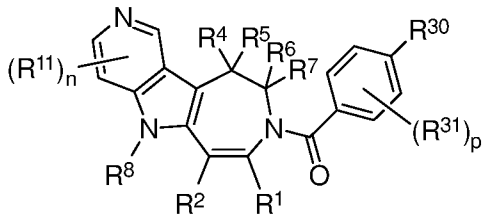
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

24. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIc):



Formula (IIc);

wherein:

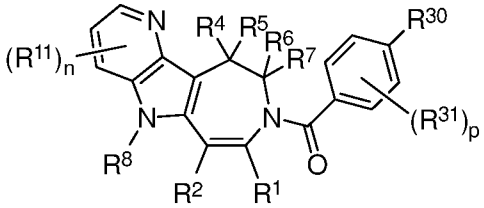
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

25. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IId):



Formula (IId);

wherein:

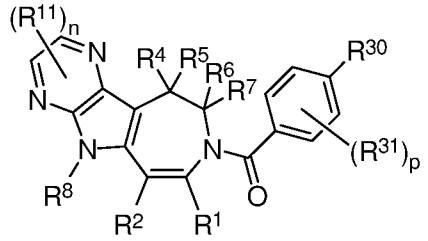
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, 2, or 3.

26. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIe):



Formula (IIe);

wherein:

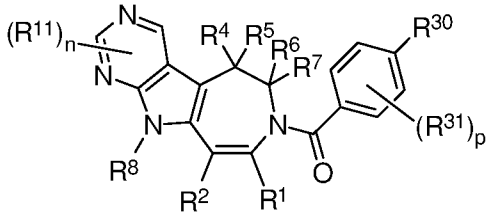
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

27. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIf):



Formula (IIf);

wherein:

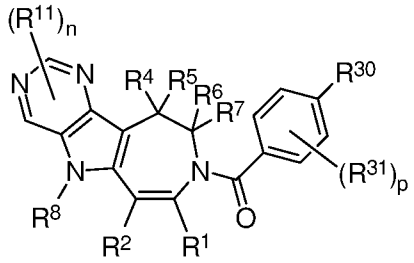
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

28. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIg):



Formula (IIg);

wherein:

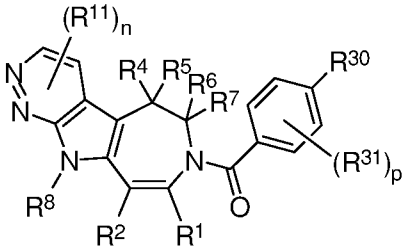
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

29. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIh):



Formula (IIh);

wherein:

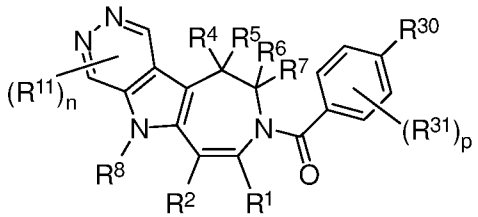
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

30. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIi):



Formula (IIi);

wherein:

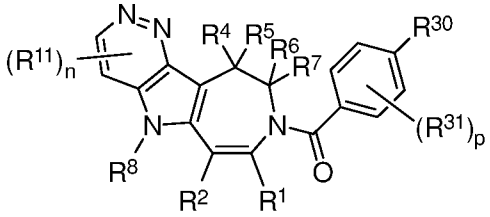
each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

31. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure of Formula (IIj):



Formula (IIj);

wherein:

each R^{11} is independently selected from the group consisting of halogen, -CN, amino, alkylamino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_8cycloalkyl, C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14};

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring; and

n is 0, 1, or 2.

32. The compound of any one of claims 22-31, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0.

33. The compound of any one of claims 22-31, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy.

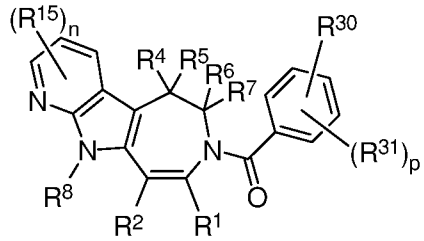
34. The compound of claim 33, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is halogen.

35. The compound of claim 33, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is C_1-C_6alkyl.

36. The compound of claim 33, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{11} is C_1-C_6alkoxy.

37. The compound of any one of claims 22-31, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 2 and each R^{11} is independently selected from the group consisting of halogen, C_1-C_6alkyl, and C_1-C_6alkoxy.

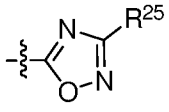
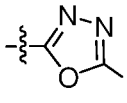
38. A compound having the structure of Formula (III), or a pharmaceutically acceptable salt, solvate, or prodrug thereof:



Formula (III);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26},  , and  ; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -

(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

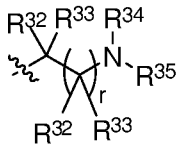
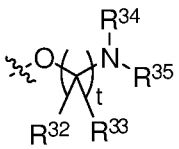
each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -$C(O)OR^{12}$, -$C(O)N(R^{13})R^{14}$, -$OC(O)OR^{12}$, -$OC(O)N(R^{13})R^{14}$, -$N(R^{13})C(O)OR^{12}$, and -$N(R^{13})C(O)N(R^{13})R^{14}$;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl,  ,  or ;

each R^{31} is independently halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

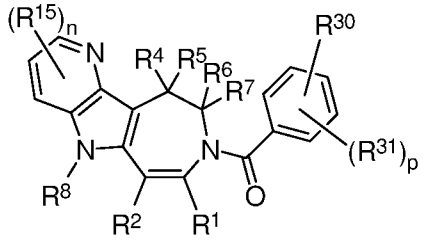
n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

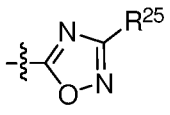
39. A compound having the structure of Formula (IV), or a pharmaceutically acceptable salt, solvate, or prodrug thereof:

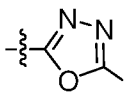


Formula (IV);

wherein:

R^1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^2 is selected from the group consisting of -CN, -C(O)OR^{25}, -C(O)N(R^{25})R^{26}, 

, and 

; or R^1 and R^2 together with the carbon atoms to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring or an optionally substituted heteroaryl ring;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl; or R^4 and R^5 together with the carbon

atom to which they are attached, form an optionally substituted C_3-C_6cycloalkyl ring or an optionally substituted C_2-C_7heterocycloalkyl ring;

R^6 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_2-C_6alkenyl, optionally substituted C_2-C_6alkynyl, and -C(O)N(R^{27})R^{28};

R^7 is selected from the group consisting of hydrogen, halogen, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_2-C_6alkenyl, and optionally substituted C_2-C_6alkynyl;

R^8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted heteroaryl, optionally substituted C_2-C_9heterocycloalkyl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

each R^{12} is independently selected from the group consisting of hydrogen and C_1-C_6alkyl;

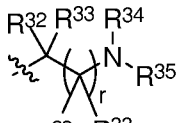
each R^{13} and R^{14} are each independently selected from the group consisting of hydrogen and C_1-C_6alkyl; or R^{13} and R^{14} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

each R^{15} is independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, -C(O)OR^{12}, -C(O)N(R^{13})R^{14}, -OC(O)OR^{12}, -OC(O)N(R^{13})R^{14}, -N(R^{13})C(O)OR^{12}, and -N(R^{13})C(O)N(R^{13})R^{14};

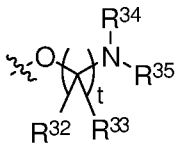
R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl);

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, optionally substituted aryl, optionally substituted -(C_1-C_2alkylene)-(aryl), optionally substituted C_2-C_9heterocycloalkyl, optionally substituted heteroaryl, and optionally substituted -(C_1-C_2alkylene)-(heteroaryl); or R^{27} and R^{28} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

R^{30} is halogen, -OH, -CN, -NO_2, -NH_2, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-



C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, heteroaryl, ,



or ;

each R^{31} is independently halogen, -OH, -CN, $-NO_2$, $-NH_2$, optionally substituted C_1-C_6alkyl, optionally substituted C_1-C_6alkoxy, optionally substituted C_1-C_6alkylamine, optionally substituted C_3-C_8cycloalkyl, optionally substituted C_2-C_9heterocycloalkyl, aryl, or heteroaryl;

each R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, halogen, and C_1-C_6alkyl;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, optionally substituted C_1-C_6alkyl, optionally substituted C_3-C_8cycloalkyl, and optionally substituted C_2-C_9heterocycloalkyl; or R^{34} and R^{35} together with the nitrogen atom to which they are attached, form an optionally substituted C_2-C_9heterocycloalkyl ring;

n is 0, 1, 2, or 3

p is 0, 1, 2, 3, or 4;

r is 0, 1, 2, 3, or 4; and

t is 2, 3, or 4.

40. The compound of claim 38 or claim 39, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 0.

41. The compound of claim 38 or claim 39, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is selected from the group consisting of halogen, optionally substituted C_1-C_6alkyl, and optionally substituted C_1-C_6alkoxy.

42. The compound of claim 41, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is halogen.

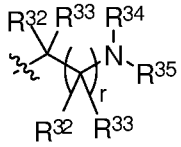
43. The compound of claim 41, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkyl.

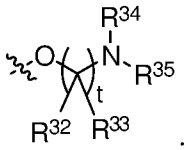
44. The compound of claim 41, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 1 and R^{15} is optionally substituted C_1-C_6alkoxy.

45. The compound of claim 38 or claim 39, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein n is 2 and each R^{15} is independently selected from the group

consisting of halogen, optionally substituted C_1-C_6alkyl, and optionally substituted C_1-C_6alkoxy.

46. The compound of any one of claims 21-45, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is F.

47. The compound of any one of claims 21-45, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is  .

48. The compound of any one of claims 21-45, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{30} is  .

49. The compound of any one of claims 21-48, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein p is 1.

50. The compound of claim 49, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{31} is halogen.

51. The compound of claim 50, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{31} is F.

52. The compound of any one of claims 21-51, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^6 and R^7 are hydrogen.

53. The compound of any one of claims 21-52, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are each independently optionally substituted C_1-C_6alkyl.

54. The compound of any one of claims 21-52, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^4 and R^5 are methyl.

55. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is $-C(O)OR^{25}$.

56. The compound of claim 55, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is optionally substituted C_1-C_6alkyl.

57. The compound of claim 56, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is methyl.

58. The compound of claim 56, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is ethyl.

59. The compound of claim 56, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is isopropyl.

60. The compound of any one of claims 1-54, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^2 is $-C(O)N(R^{25})R^{26}$.

61. The compound of claim 60, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is optionally substituted C_1-C_6alkyl.

62. The compound of claim 61, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is methyl.

63. The compound of claim 61, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is ethyl.

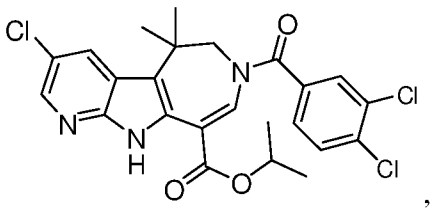
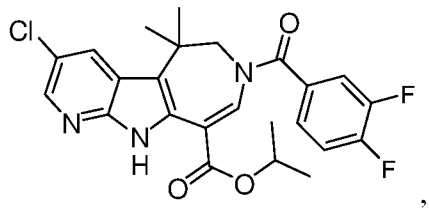
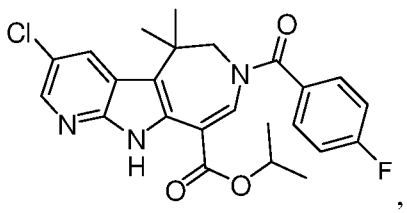
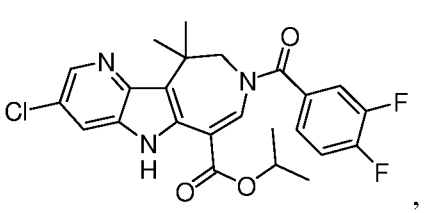
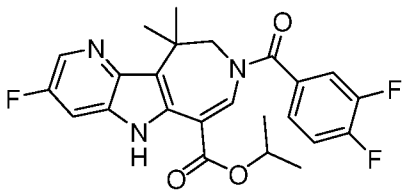
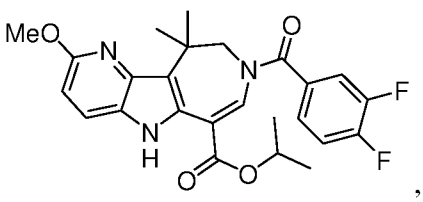
64. The compound of claim 61, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{25} is isopropyl.

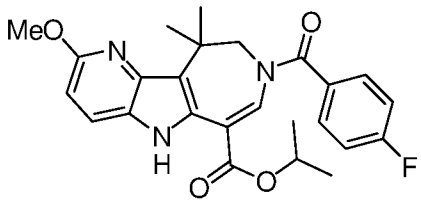
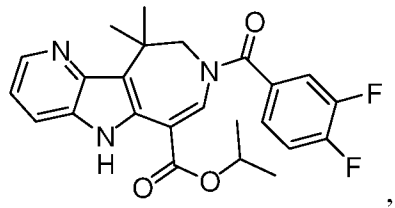
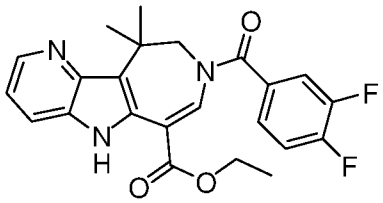
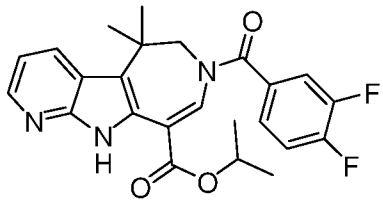
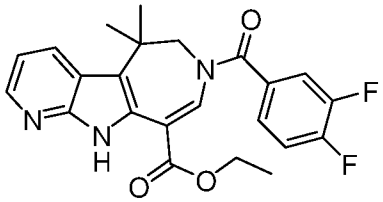
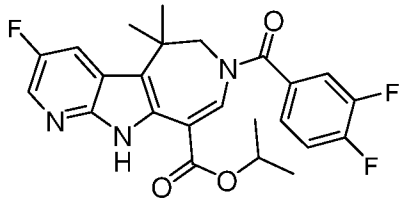
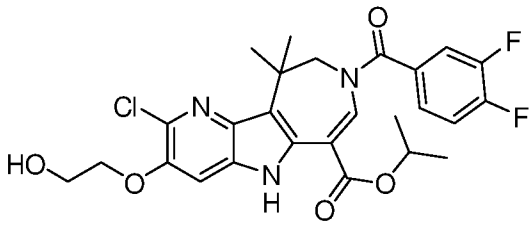
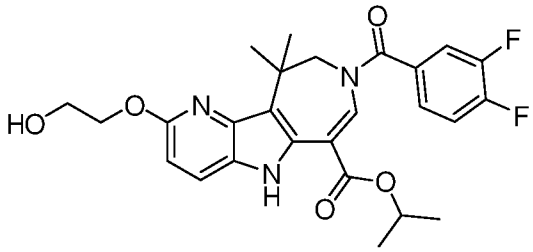
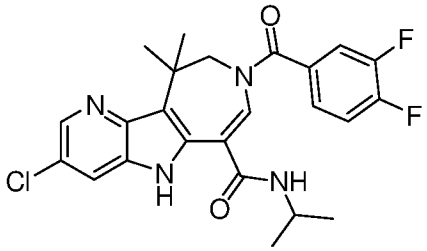
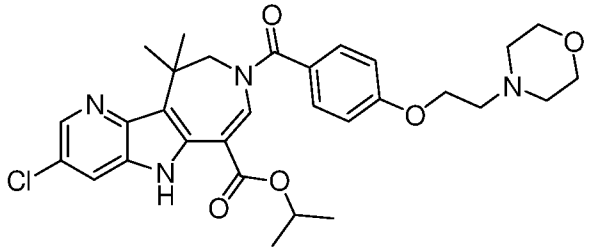
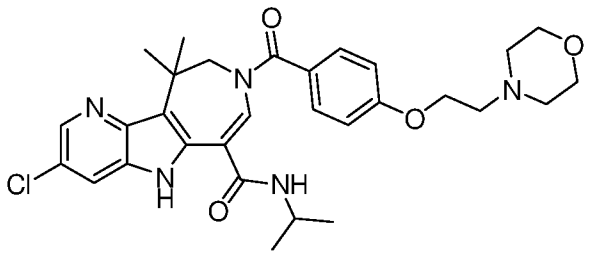
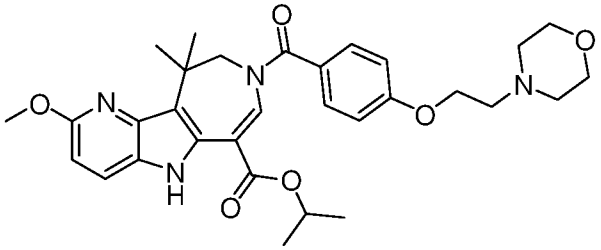
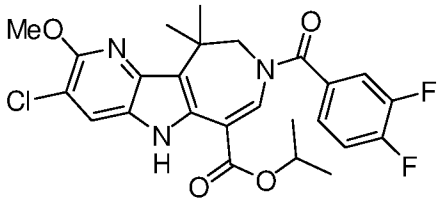
65. The compound of any one of claims 60-64, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^{26} is hydrogen.

66. The compound of any one of claims 1-65, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^1 is hydrogen.

67. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein R^8 is hydrogen.

68. A compound having the structure:


,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

, or

; or a pharmaceutically acceptable salt, or pharmaceutically acceptable solvate thereof.

69. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, excipient or binder, and a compound of any one of claims 1-68; or a pharmaceutically acceptable salt or solvate thereof.

70. A method of treating a disease, disorder or condition in a mammal that would benefit from farnesoid X receptor (FXR) modulation comprising administering to the mammal a compound, or a pharmaceutically acceptable salt, or solvate thereof, according to any one of claims 1-68.

71. A method of modulating FXR activity comprising contacting FXR, or portion thereof, with a compound, or a pharmaceutically acceptable salt, or solvate thereof, according to any one of claims 1-68.

72. The method of claim 71, wherein the disease, disorder or condition in a mammal is selected from nonalcoholic steatohepatitis (NASH), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events, atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis and obesity.

73. The method of claim 72, wherein the disease or disorder is nonalcoholic steatohepatitis (NASH).

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/002549

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/14 A61K31/407 A61P3/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/009387 A2 (X CEPTOR THERAPEUTICS INC [US]; MARTIN RICHARD [US]; WANG TIE-LIN [US]) 3 February 2005 (2005-02-03) Examples 4, 5, 9, 10;; claim 1 -----	1-73
X	WO 2007/070796 A1 (EXELIXIS INC [US]; BAIK TAEGON [US]; BUHR CHRIS A [US]; BUSCH BRETT B) 21 June 2007 (2007-06-21) examples;; claim 1 -----	1-73

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2016	08/03/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/002549

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005009387 A2	03-02-2005	AU 2004259009 A1	03-02-2005
		BR PI0412262 A	19-09-2006
		CA 2532798 A1	03-02-2005
		CN 1852748 A	25-10-2006
		CR 8258 A	30-08-2006
		EC SP066392 A	26-01-2007
		EP 1648408 A1	26-04-2006
		JP 4679517 B2	27-04-2011
		JP 2006528637 A	21-12-2006
		KR 20060052867 A	19-05-2006
		US 2007015746 A1	18-01-2007
		WO 2005009387 A2	03-02-2005
WO 2007070796 A1	21-06-2007	AR 058781 A1	20-02-2008
		AU 2006325815 A1	21-06-2007
		BR PI0620156 A2	20-12-2011
		CA 2633243 A1	21-06-2007
		EC SP088623 A	29-08-2008
		EP 1963331 A1	03-09-2008
		JP 5420908 B2	19-02-2014
		JP 2009519964 A	21-05-2009
		JP 2014028829 A	13-02-2014
		PE 11002007 A1	21-12-2007
		US 2009203577 A1	13-08-2009
		WO 2007070796 A1	21-06-2007