identifier NCT03941483). To date, however, no PPARδ agonist has been approved and marketed as a treatment for AKI.

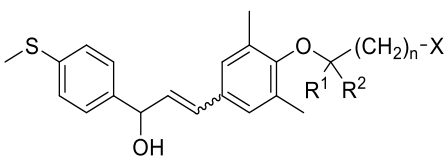
[0009] There remains a need for new preventions and treatments for liver disorders, kidney disorders and other conditions associated with PPARs.

4. SUMMARY

[0010] The present disclosure provides novel compounds and their use to treat various disorders, for example, liver disorders such as NASH, kidney disorders such as AKI, and other conditions associated with PPARs. Without being bound by theory, the inventor believes that the clinical usefulness of PPAR agonists such as elafibranor are limited by their toxicity such that doses often cannot be increased sufficiently to reach an effective dose. The subject invention provides novel compounds, including derivatives of elafibranor and related compounds, and derivatives of PPAR modulators described in WO 2011/020001, WO 2017/06246, WO 2017/180818, and WO 2018/067857. Without being bound by theory, the inventor believes that the compounds described herein can act as PPAR agonists and/or as PPAR agonist prodrugs, which have advantageous properties that result in improved bioavailability and/or half-life and/or safety and/or efficacy and/or improved therapeutic indexes, following administration. In particular, the compound may thus have an improved therapeutic index. The therapeutic index (TI) is a ratio that compares the dose at which a compound becomes toxic against the dose at which it is effective. One common measure of TI is TD_{50}/ED_{50}, wherein TD_{50} and ED_{50} are the toxic and effective doses, respectively, for 50% of the population. The larger the TI, the safer a compound is. Compounds with a low TI can be difficult to use in clinical practice and often require monitoring of plasma concentration in order to prevent toxicity. The one or more advantageous properties of the compounds of the disclosure (compared to known PPAR agonists, such as elafibranor or one or more PPAR agonists described in WO 2011/020001, WO 2011/020001, WO 2017/06246, WO 2017/180818, and/or WO 2018/067857) can include, for example, better solubility, better kinetics, better absorption, better PPAR receptor selectivity at pharmaceutically effective doses, reduced drug metabolism by cytochrome P450 or other enzymes such as reductases, reduced glucuronidation, reduced toxicity, or a combination thereof.

[0011] There is provided compounds of Formula (A)-(H) and (J)-(AA) and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

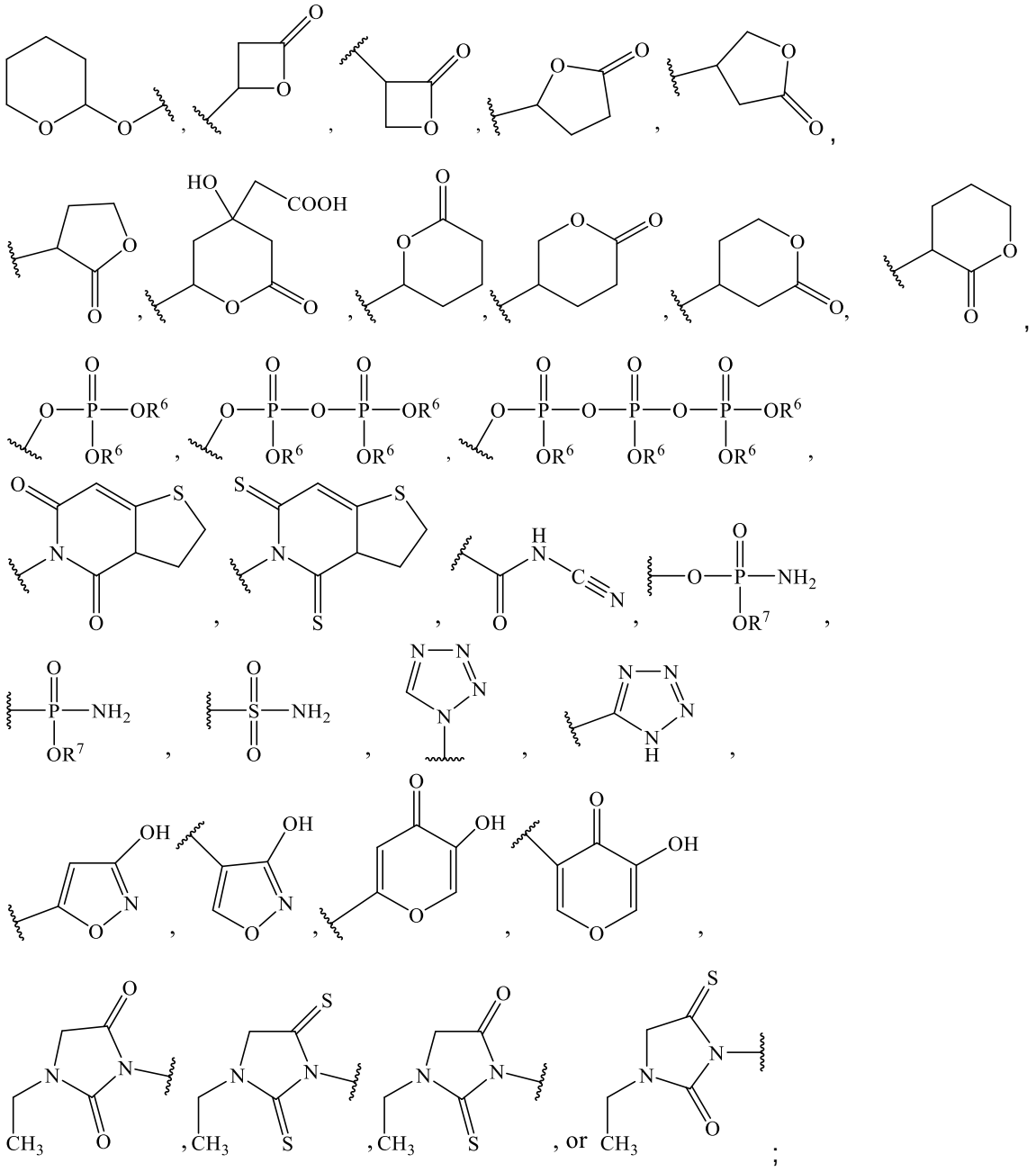
[0012] In one example, the present disclosure provides compounds of Formula (A):



(A), and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof, wherein:

each R^1 and R^2 is independently -C_1–C_6 alkyl, -C_2–C_6 alkenyl, -C_2–C_6 alkynyl, phenyl, or benzyl; or alternatively, R^1 and R^2 together with the carbon atom to which R^1 and R^2 are attached form a C_3–C_7 cycloalkyl group;

X is -CH_2OH, -COOH, -COH, -$COOR^3$, -$COOCH_2CONR^4R^5$, -SO_3H,



R^3 is -C_1–C_6 alkyl, -C_2–C_6 alkenyl, -C_2–C_6 alkynyl, phenyl, or benzyl;

each R^4 and R^5 is independently alkyl, aryl, or heteroaryl; or alternatively, R^4 and R^5 together with the carbon atom to which R^4 and R^5 are attached form a heterocycle;

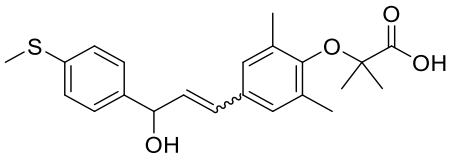
each R^6 and R^7 is independently H, -C_1–C_6 alkyl, -C_2–C_6 alkenyl, or -C_2–C_6 alkynyl; and

n is 0, 1, 2, 3, or 4.

[0013] In another example, the present disclosure also provides compounds of Formula (B)

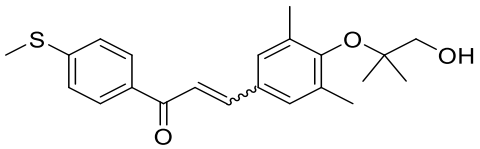
each R^6 and R^7 is independently H, -C_1–C_6 alkyl, -C_2–C_6 alkenyl, or -C_2–C_6 alkynyl; and
n is 0, 1, 2, 3, or 4.

[0014] In another example, there is provided 2-(4-(3-hydroxy-3-(4-(methylthio)phenyl)prop-1-en-1-yl)-2,6-dimethylphenoxy)-2-methylpropanoic acid ("Compound I") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs, thereof, wherein Compound I has the structure:



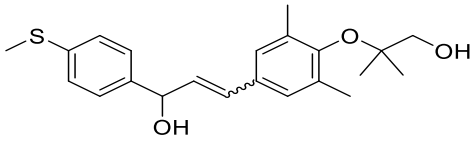
(I).

[0015] In another example, there is provided 3-(4-((1-hydroxy-2-methylpropan-2-yl)oxy)-3,5-dimethylphenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-one ("Compound II") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof, wherein Compound II has the structure:



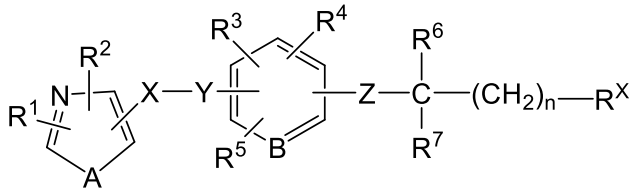
(II).

[0016] In another example, there is provided 3-(4-((1-hydroxy-2-methylpropan-2-yl)oxy)-3,5-dimethylphenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-ol ("Compound III") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof, wherein Compound III has the structure



(III).

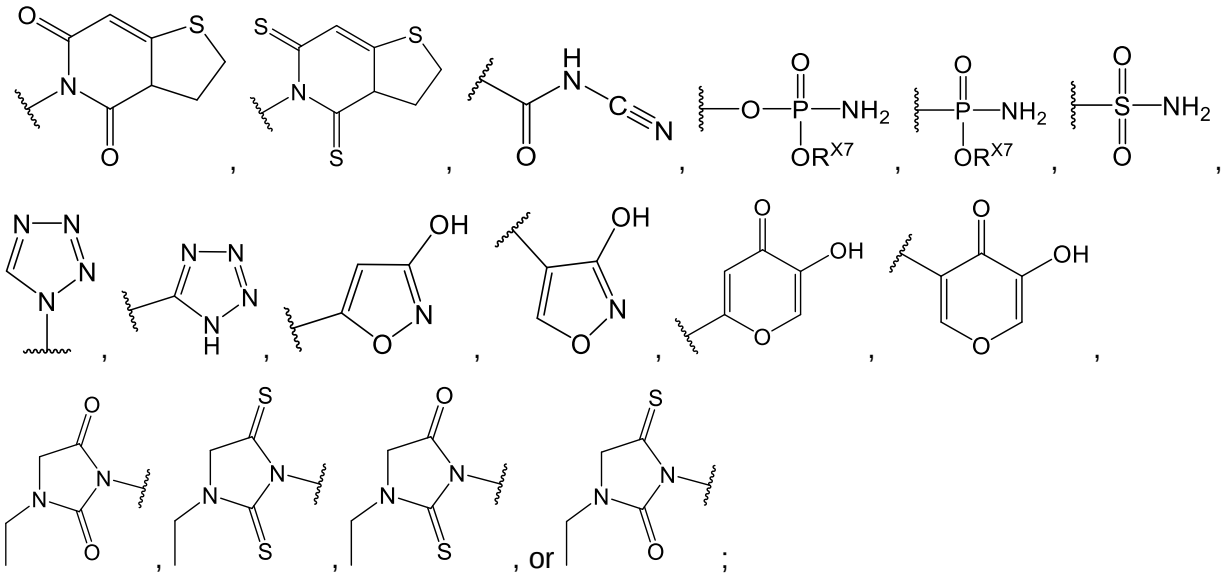
[0017] In one aspect, the present disclosure provides a compound of Formula (C)



(C)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof wherein:

R^1 is phenyl, naphthyl, pyridyl, thienyl, furyl, quinolyl or benzothienyl, any of which is unsubstituted or substituted with C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, C_{2-8} alkenyl, C_{2-8} alkynyl, halogen, C_{2-7} acyl, benzoyl, hydroxyl, nitro, amino, phenyl or pyridyl;



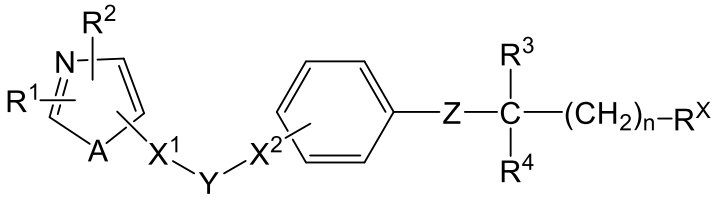
each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018] In other examples, the disclosure provides compounds of Formula (D)-(H) and (J)-(AA) and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

[0018a] In another aspect, the present disclosure provides a compound of Formula (D):



(D)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of R^1 and R^2 independently is a hydrogen, a halogen, nitro, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl having 1 to 3 halogens, C_{1-8} haloalkoxy having 1 to 3 halogens, C_{2-8} alkenyl, C_{2-8} alkynyl, 3-7 membered cycloalkyl, C_{1-8} alkyl substituted with 3-7 membered cycloalkyl, C_{6-10} aryl which is optionally substituted, arylalkyl group which has a C_{6-10} aryl moiety and C_{1-8} alkyl moiety, a heterocyclic group or a heterocyclic-alkyl group having a C_{1-8} alkyl group;

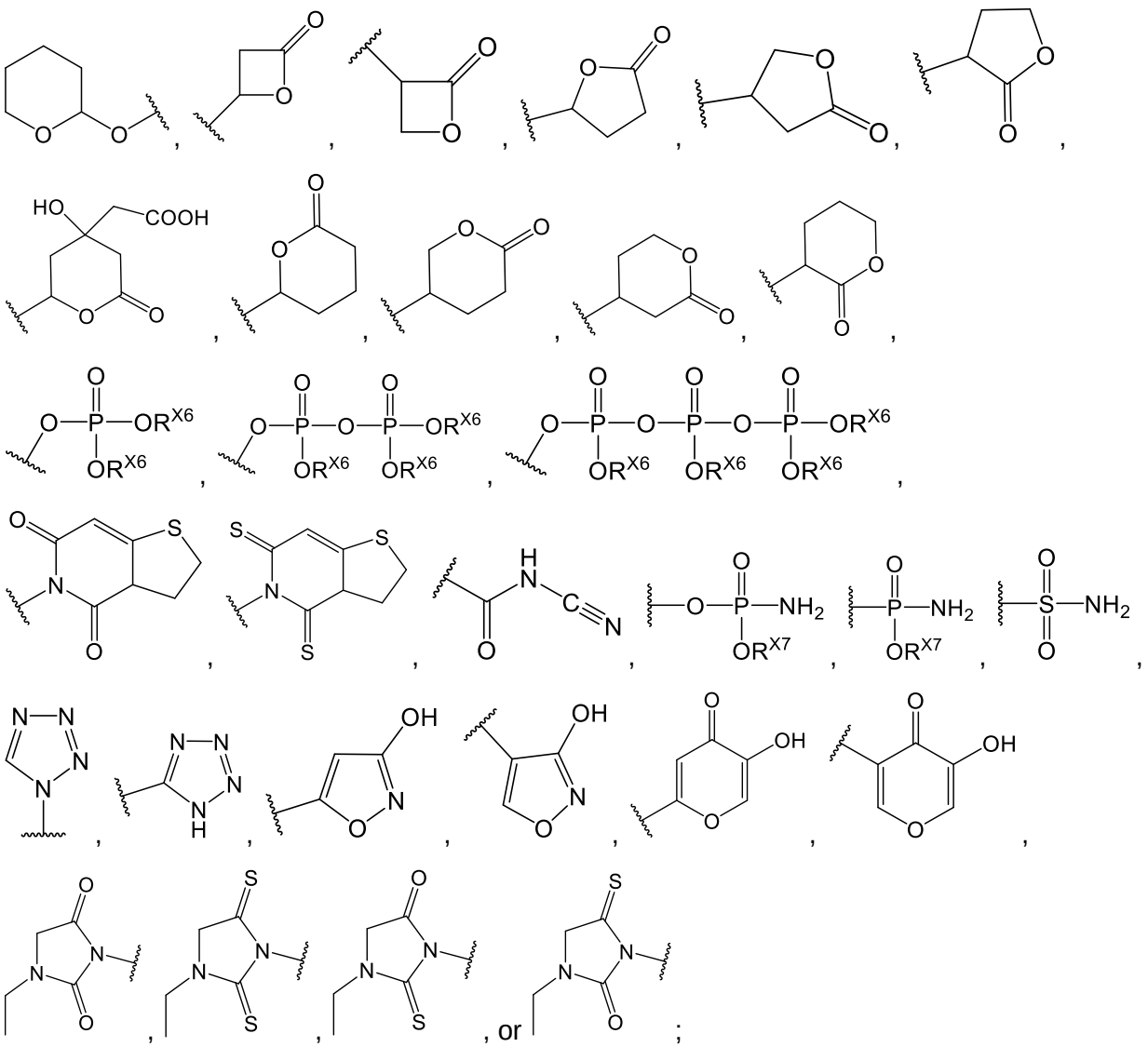
each occurrence of R^3, R^4, and R^5 is independently a hydrogen or C_{1-8} alkyl;

A is an oxygen atom, a sulfur atom, or NR^3;

each of X^1, X^2, and Z independently is C(=O), C(=O)NH, C(=N-OR^4), CH(OR^5), NH(C=O), $NHSO_2$, SO_2NH, CH=CH, C≡C, or a bond; and

Y is C_{1-8} alkylene;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

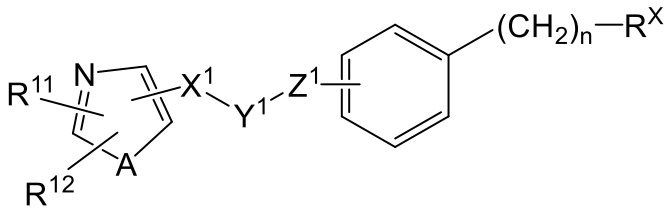


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018b] In another aspect, the present disclosure provides a compound of Formula (E):



(E)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

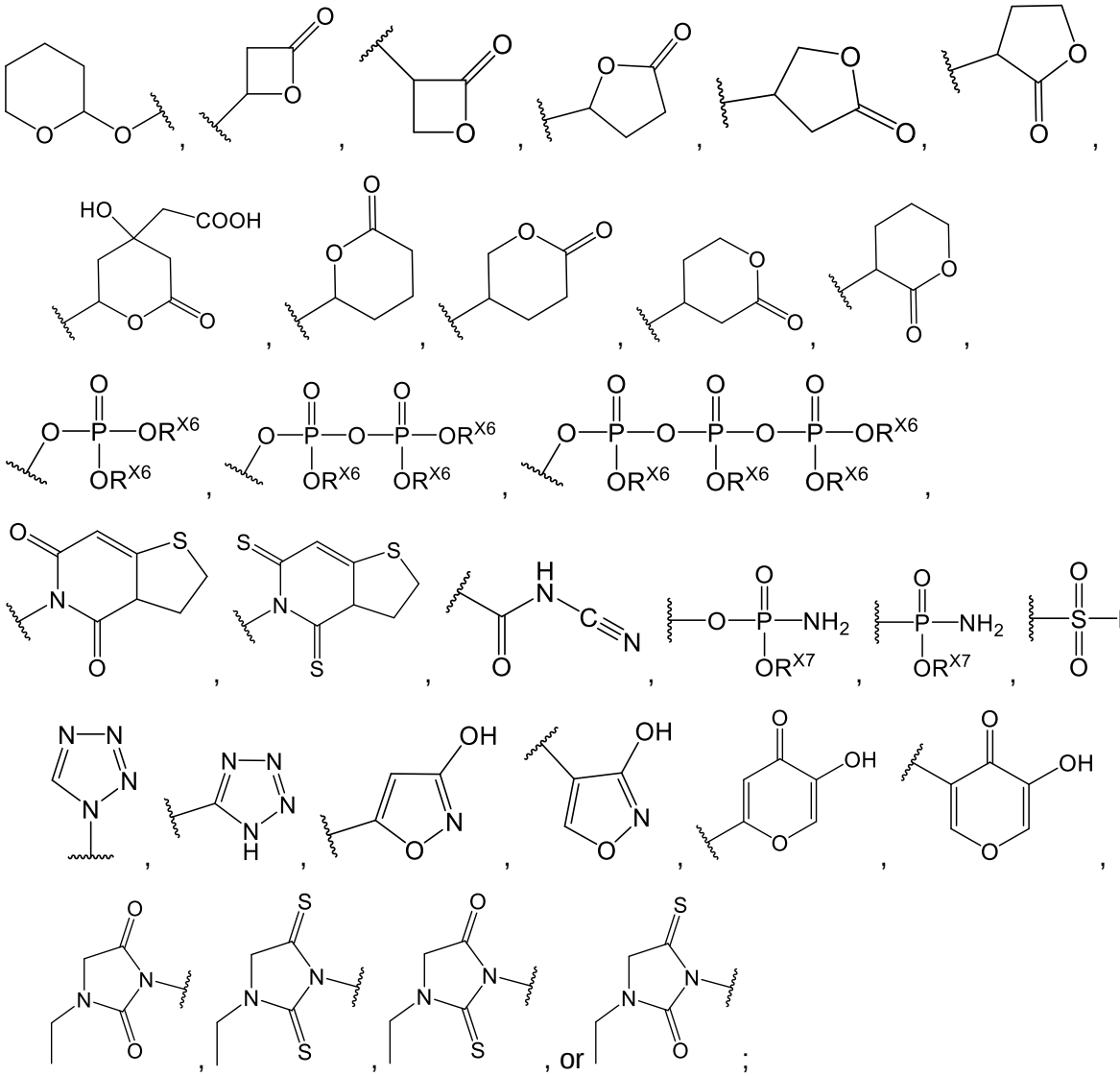
each of R^{11} and R^{12} independently is hydrogen, halogen, nitro, hydroxyl, amino, C_{1-8} alkyl, an C_{1-8} alkoxy, C_{1-8} haloalkyl group having 1 to 3 halogens, C_{1-8} haloalkoxy group having 1 to 3 halogens, C_{2-8} alkenyl, C_{2-8} alkynyl, a 3-7 membered cycloalkyl, C_{1-8} alkyl having a 3-7

membered cycloalkyl substituent, or phenyl, naphthyl, benzyl, phenethyl, pyridyl, thienyl, furyl, quinolyl, or benzothienyl group which optionally has a substituent which is a halogen atom, nitro, hydroxyl, amino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl having 1 to 3 halogens, C_{1-8} haloalkoxy having 1 to 3 halogens, C_{2-8} alkenyl, C_{2-8} alkynyl, 3-7 membered cycloalkyl group, C_{1-8} alkyl group having a 3-7 membered cycloalkyl substituent, phenyl or pyridyl;

each of X^1 and Z^1 independently is C(=O), C(=O)NH, C(=N-OR^{14}), CH(OR^{15}), NH(C=O), $NHSO_2$, SO_2NH, CH=CH, C≡C, or a bond, wherein each of R^{14} and R^{15} is a hydrogen or C_{1-8} alkyl;

Y^1 is C_{1-8} alkylene;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

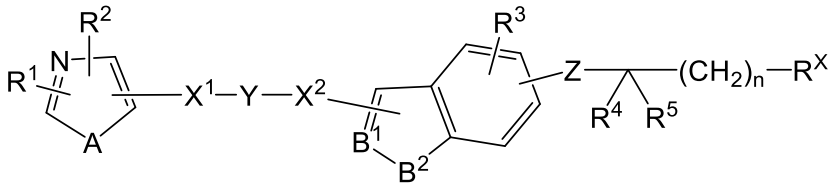


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018c] In another aspect, the present disclosure provides a compound of Formula (F):



(F)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

A is O, S or NR^7 in which R7 is hydrogen or C_{1-8} alkyl;

B^1 is CW or N in which W is hydrogen or a bond; B^2 is O, S or NR^8 in which R^8 is hydrogen or C_{1-8} alkyl;

each of X^1 and X^2 is O, S, NH, NHC(=O), C(=O), C(=N-OR^9), CH(OR^{10}), C=C, C≡C or a bond, wherein each of R^9 and R^{10} is hydrogen or C_{1-8} alkyl;

Y is C_{1-8} alkylene, which is unsubstituted or substituted with C_{1-8} alkyl or C_{1-8} haloalkyl having 1-3 halogens;

Z is NH, O or S;

R^1 is aryl, which is unsubstituted or substituted with C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl having 1-3 halogens, hydroxyl, nitro, amino, phenyl, pyridyl or halogen, or a heterocyclic group having a five to eight membered ring comprising one to three hetero atoms each of which is independently nitrogen, oxygen or sulfur and the other atoms are carbon, optionally wherein a benzene ring is condensed with the heterocyclic ring;

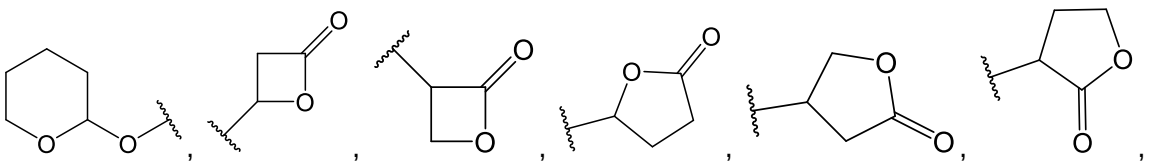
R^2 is C_{2-8} alkyl, C_{1-8} haloalkyl having with 1-3 halogens, C_{3-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl substituted with aryl, which is unsubstituted or substituted with C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl having 1-3 halogens, hydroxyl, nitro, amino, phenyl, pyridyl or halogen, or C_{1-4} alkyl substituted with a heterocyclic group having five to eight membered ring having one to three heteroatoms each of which is independently nitrogen, oxygen or sulfur;

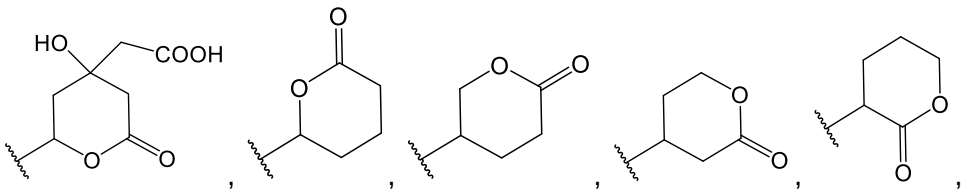
R^3 is halogen, trifluoromethyl, C_{1-8} alkyl, C_{2-8} alkenyl or C_{2-8} alkynyl;

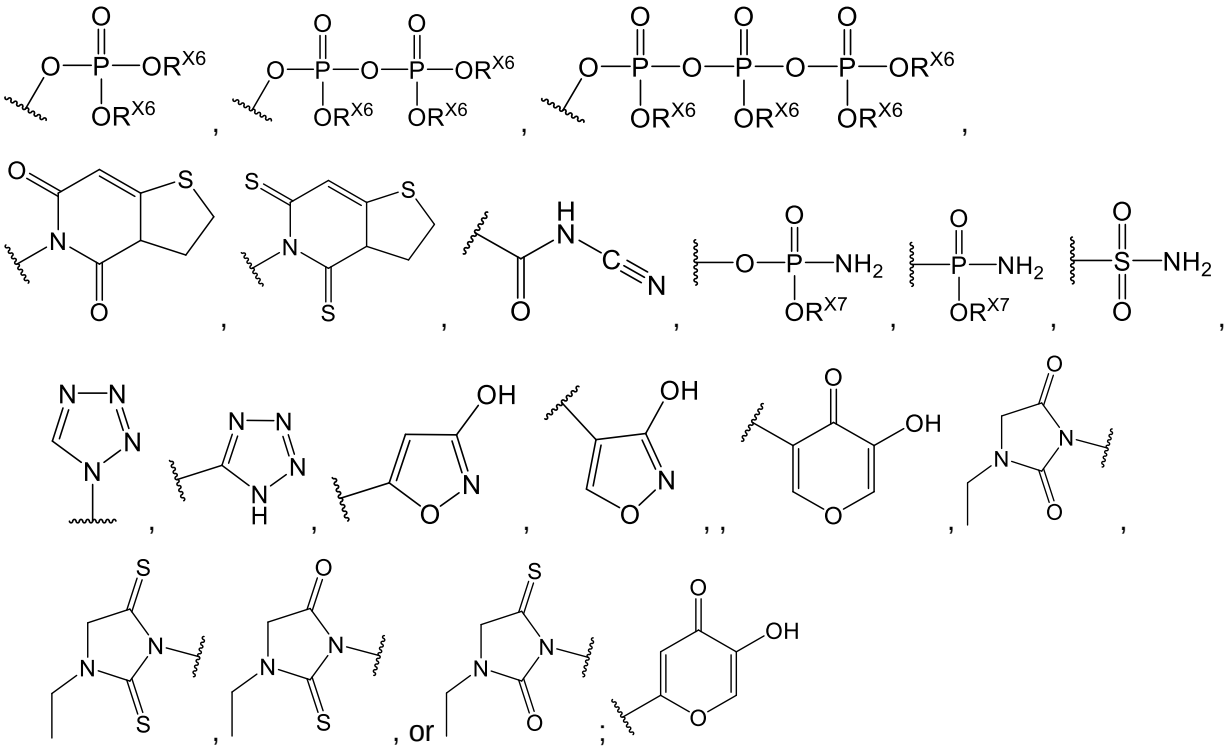
each of R^4 and R^5 is hydrogen, C_{1-8} alkyl or C_{1-8} haloalkyl having 1-3 halogens;

each of Z and R^3 is attached to the benzene ring, and X^2 is not attached to the benzene ring;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,





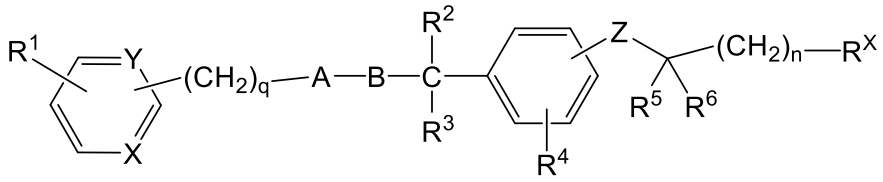


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018d] In another aspect, the present disclosure provides a compound of Formula (G):



(G)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of R^1 and R^4, which are the same or different, is a hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl; C_{1-8} haloalkoxy; hydroxyl, nitro, C_{2-8} acyl group, C_{6-10} aryl, or a 5- or 6-membered heterocyclic group;

R^2 is hydrogen;

R^3 is C_{1-8} alkyl, or R^3 is combined with R^2 to form =O or =C(R^7)(R^8) in which each of R^7 and R^8, which are the same or different, is a hydrogen or C_{1-8} alkyl;

each of R^5 and R^6, which are the same or different, is a hydrogen atom, C_{1-8} alkyl, C_{1-8} haloalkyl;

X and Y are the same or different and each represents CH or N;

Z is oxygen or sulfur;

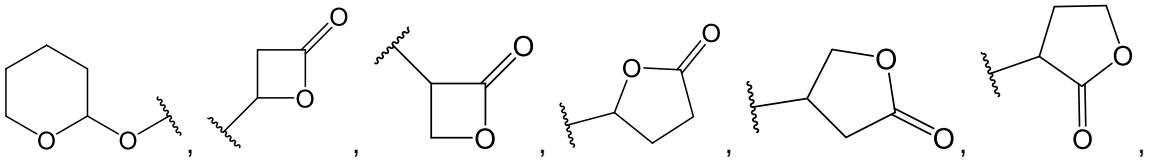
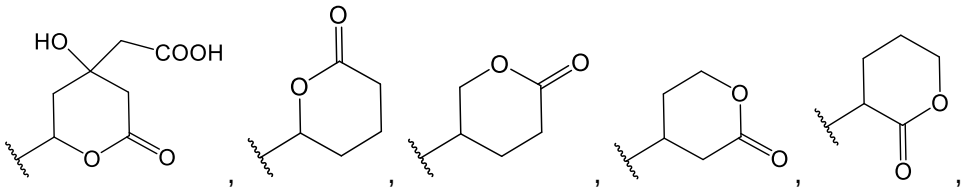
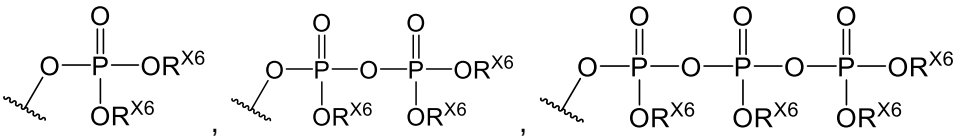
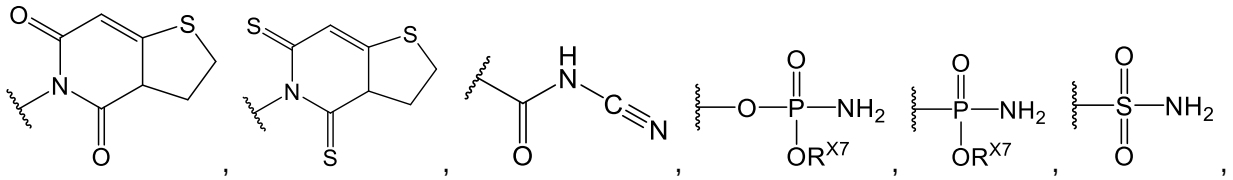
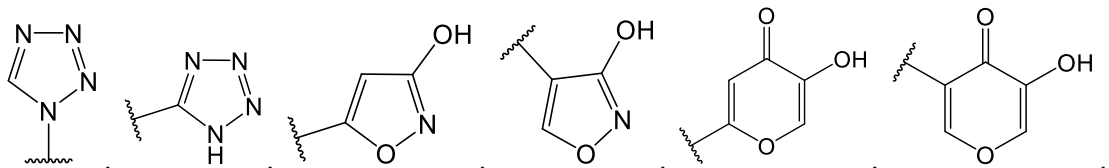
A is a 5-membered heterocyclic group which is pyrazole, thiophene, furan or pyrrole, wherein the heterocyclic group is unsubstituted or substituted with C_{1-8} alkyl having a substituent which is C_{1-8} alkyl, 3- to 7-membered cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8}

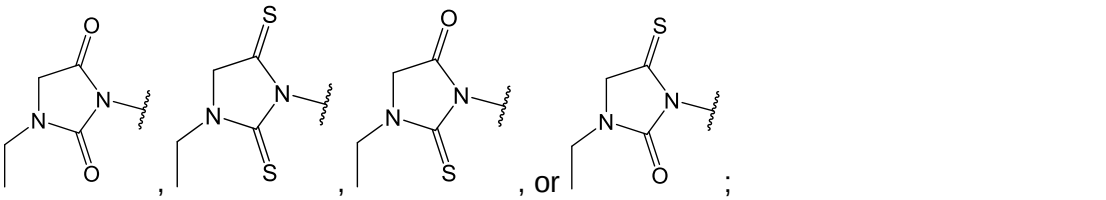
alkyl group substituted with a 3- to 7-membered cycloalkyl group, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or 5- or 6-membered heterocyclic group;

B is a C_{1-8} alkylene chain which is unsubstituted or substituted with C_{1-8} alkyl, 3- to 7-membered cycloalkyl group, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl or C_{1-8} haloalkoxy, the alkylene group optionally having a double bond in the case that the alkylene group has 2 to 6 carbon atoms;

q is 0, 1, 2, 3, 4, or 5;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

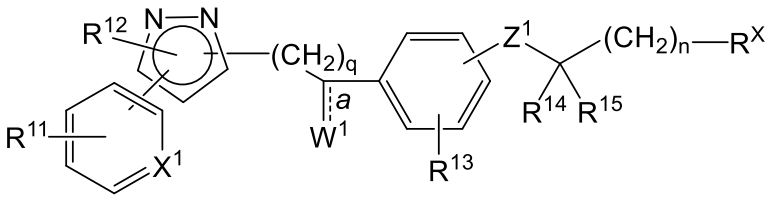


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018e] In another aspect, the present disclosure provides a compound of Formula (H):



(H)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of R^{11} and R^{13}, which are the same or different, is a hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl; C_{1-8} haloalkoxy; hydroxyl, nitro, C_{2-8} acyl group, C_{6-10} aryl, or a 5- or 6-membered heterocyclic group;

R^{12} is hydrogen, C_{1-8} alkyl, a 3- to 7-membered cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl group substituent, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or a C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

R^{14} and R^{15} are the same or different and each is a hydrogen atom, C_{1-8} alkyl, or C_{1-8} haloalkyl;

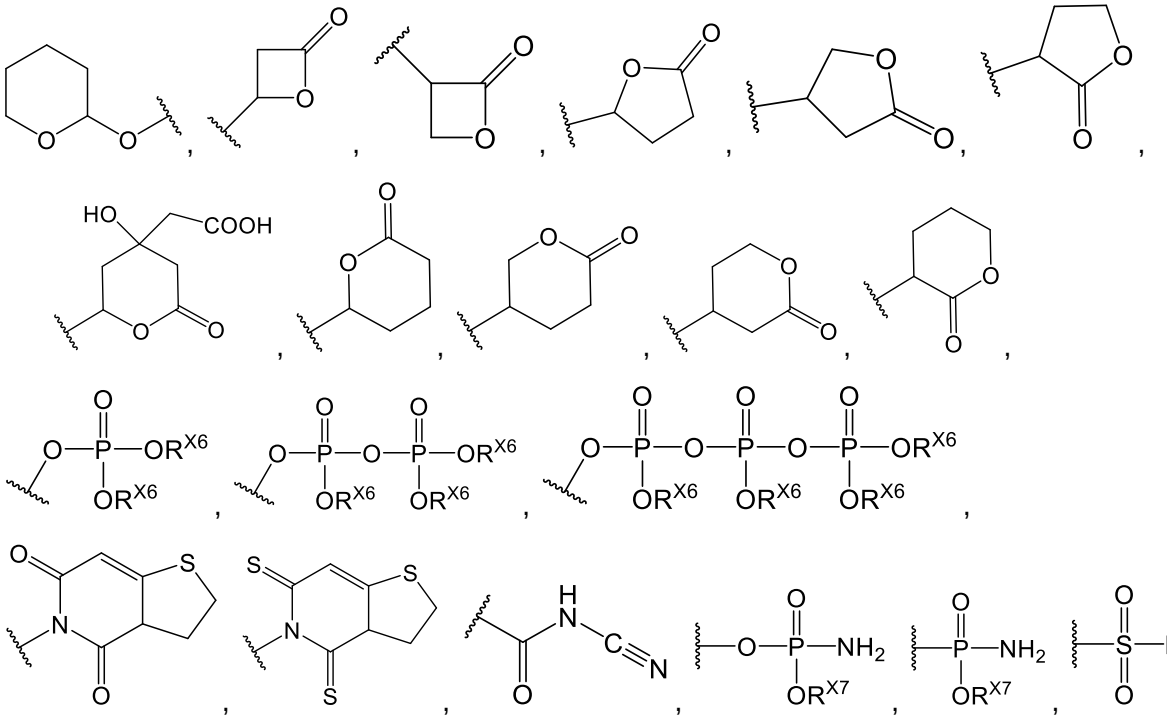
X^1 is CH or N;

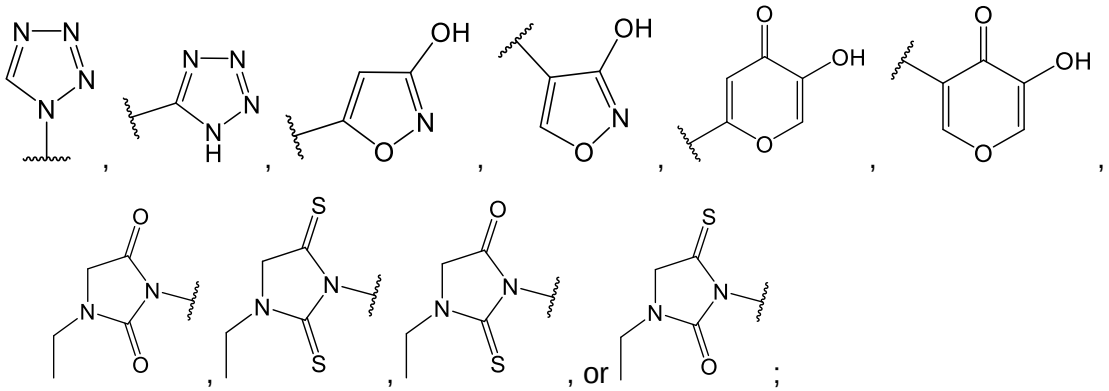
Z^1 is oxygen or sulfur;

W^1 is oxygen or CH_2 when bond *a* is present and OH when bond *a* is absent;

q is 2, 3, or 4.

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



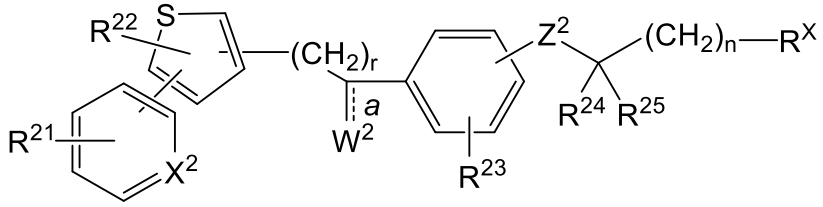


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018f] In another aspect, the present disclosure provides a compound of Formula (J):



(J)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of R^{21} and R^{23}, which are the same or different, is a hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl; C_{1-8} haloalkoxy; hydroxyl, nitro, C_{2-8} acyl group, C_{6-10} aryl, or a 5- or 6-membered heterocyclic group;

R^{22} is hydrogen, C_{1-8} alkyl, a 3- to 7-membered cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl group substituent, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or a C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

R^{24} and R^{25} are the same or different and each is a hydrogen atom, C_{1-8} alkyl, or C_{1-8} haloalkyl;

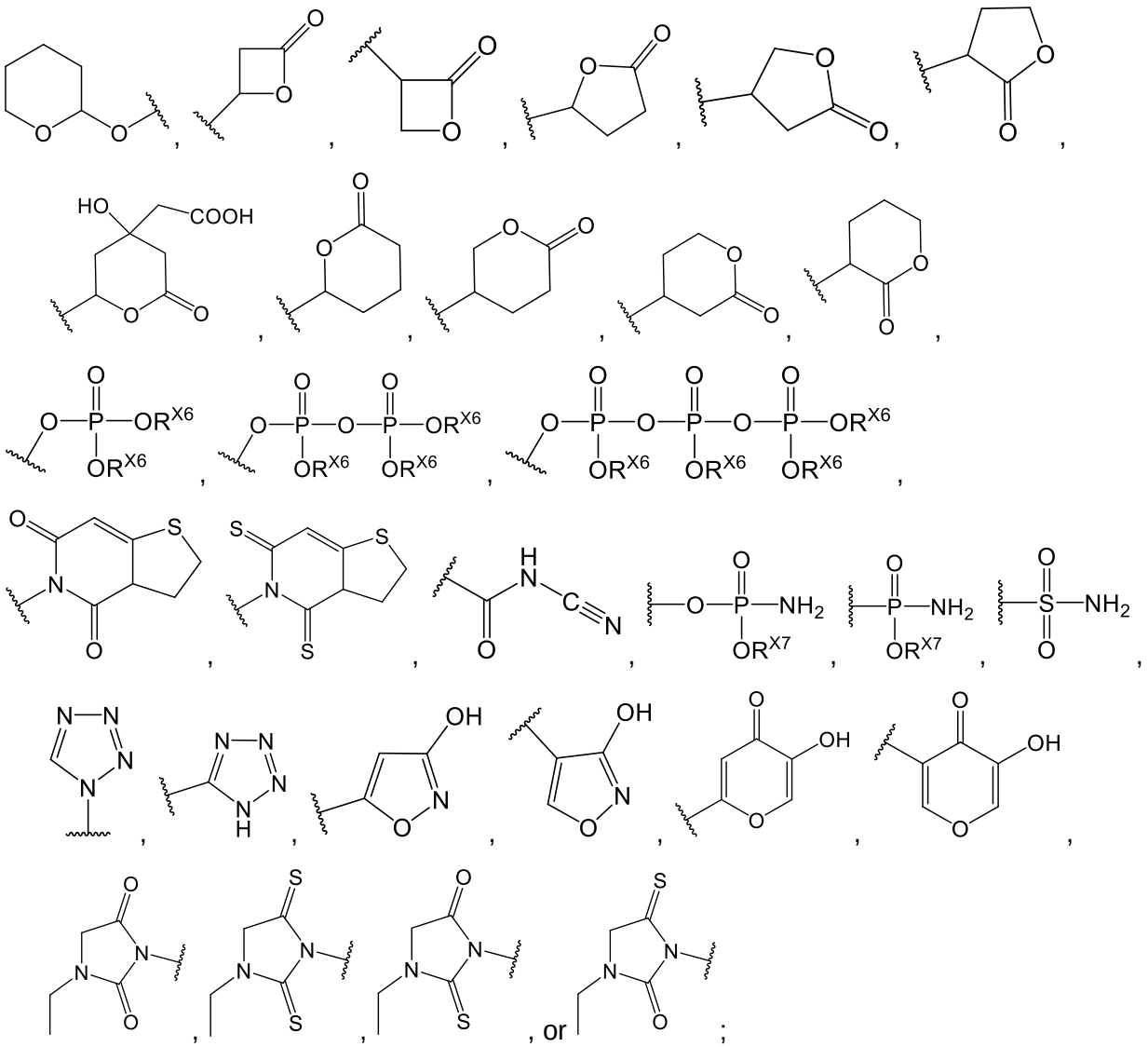
X^2 is CH or N;

Z^2 is oxygen or sulfur;

W^2 is oxygen or CH_2 when bond *a* is present and OH when bond *a* is absent;

r is 2, 3, or 4.

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

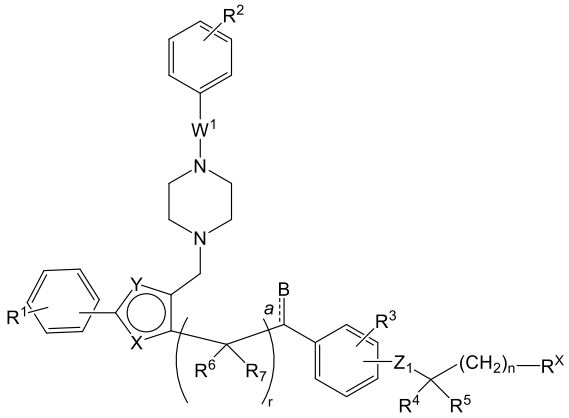


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018g] In another aspect, the present disclosure provides a compound of Formula (K):



(K)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

A is CH or nitrogen;

B, when bond *a* is present, is oxygen or $C(R^8)(R^9)$ in which each of R^8 and R^9 is independently hydrogen or $C_{1\text{-}8}$ alkyl; B, when bond *a* is absent, is OH;

W^1 is a bond, C(=O), or $(C(R^{10})(R^{11}))_m$ in which each of R^{10} and R^{11} is independently a hydrogen or $C_{1\text{-}8}$ alkyl group and m is 1, 2, or 3;

X and Y differ from each other, and each is an oxygen atom, a sulfur atom, a nitrogen atom, or CR^{12} in which R^{12} is a hydrogen or $C_{1\text{-}8}$ alkyl;

Z^1 is a bond, oxygen, sulfur, or $C(R^{13})(R^{14})$ in which each of R^{13} and R^{14} is independently a hydrogen or $C_{1\text{-}8}$ alkyl;

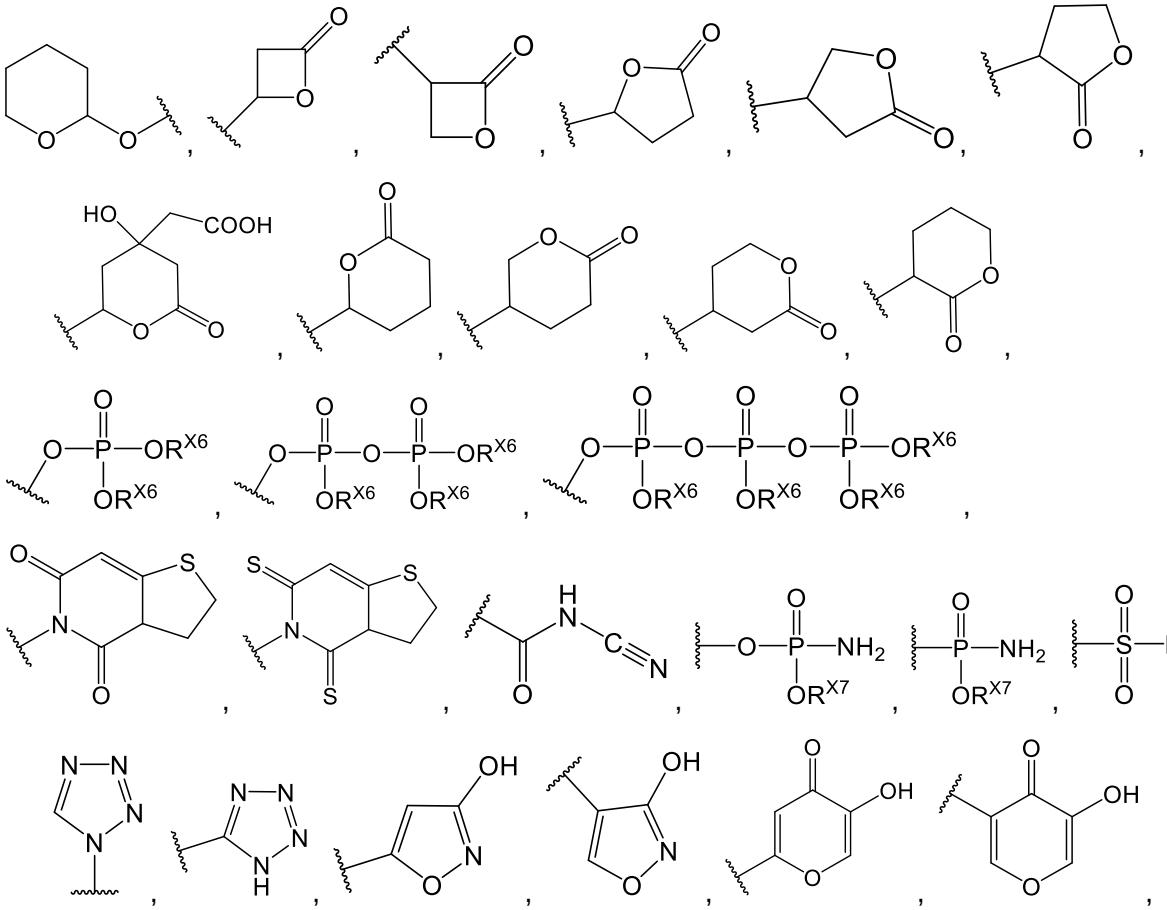
each of R^1, R^2, and R^3, is independently a hydrogen, $C_{1\text{-}8}$ alkyl, $C_{2\text{-}8}$ alkenyl, $C_{2\text{-}8}$ alkynyl, $C_{1\text{-}8}$ alkoxy, halogen, $C_{1\text{-}8}$ haloalkyl; $C_{1\text{-}8}$ haloalkoxy; hydroxyl, nitro, $C_{2\text{-}8}$ acyl group, $C_{6\text{-}10}$ aryl, or a 5- or 6-membered heterocyclic group;

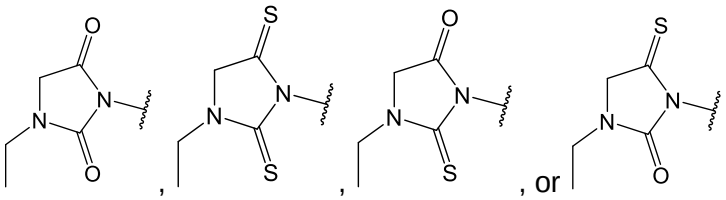
each of R^4 and R^5 is independently hydrogen, $C_{1\text{-}8}$ alkyl, $C_{1\text{-}8}$ haloalkyl;

each of R^6 and R^7 is independently hydrogen, $C_{1\text{-}8}$ alkyl, $C_{2\text{-}8}$ alkenyl, $C_{2\text{-}8}$ alkynyl, or $C_{1\text{-}8}$ haloalkyl

r is 1, 2, 3, 4, or 5;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



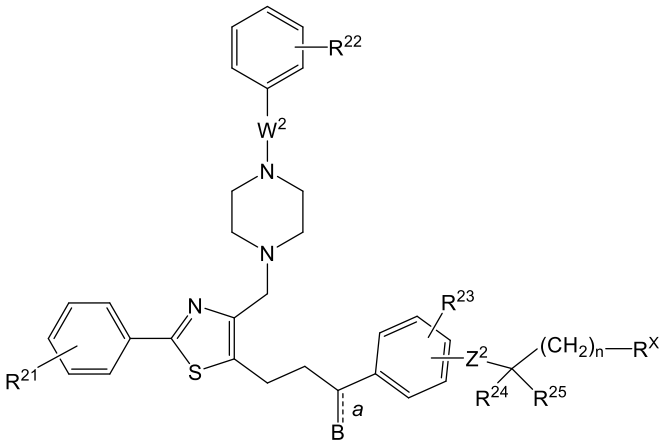


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018h] In another aspect, the present disclosure provides a compound of Formula (L):



(L)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

B, when bond *a* is present, is oxygen; B, when bond *a* is absent, is OH;

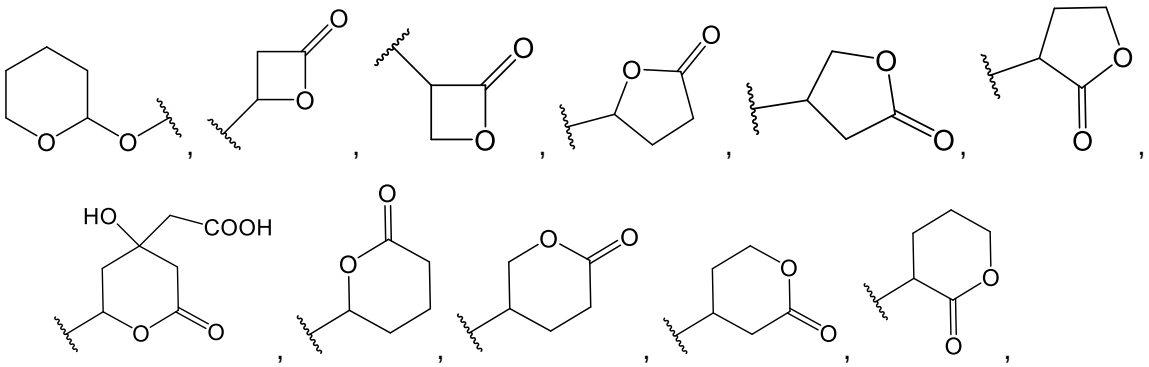
W^2 is a bond, C(=O), or CH_2;

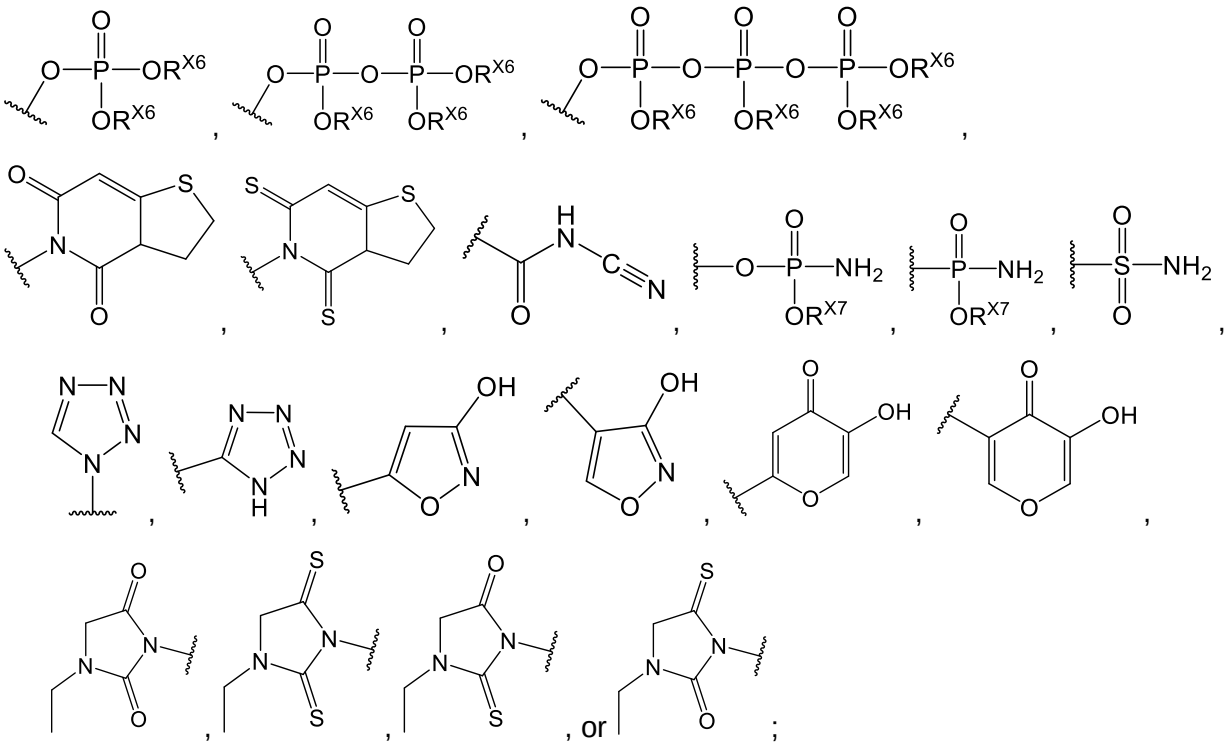
Z^2 is oxygen or sulfur;

each of R^{21}, R^{22}, and R^{23} is independently a hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl; C_{1-8} haloalkoxy; hydroxyl, nitro, C_{2-8} acyl group, C_{6-10} aryl, or a 5- or 6-membered heterocyclic group;

each of R^{24} and R^{25} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



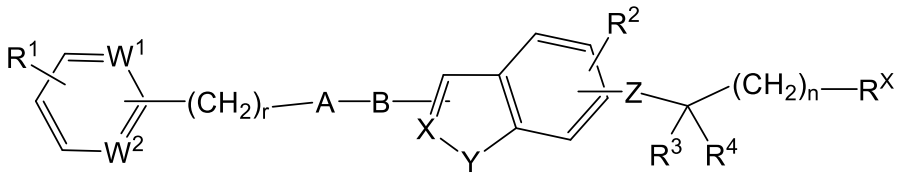


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018i] In another aspect, the present disclosure provides a compound of Formula (M):



(M)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of W^1 and W^2 is independently nitrogen or CH;

X is nitrogen or CH;

Y is oxygen or sulfur;

Z is a bond, oxygen, sulfur or NR^5, in which R^5 is hydrogen or C_{1-8} alkyl;

each of R^1 and R^2 is independently hydrogen, halogen, hydroxyl, nitro, amino, C_{1-8} alkyl, 3- to 7-membered cycloalkyl group, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, 5- or 6-membered heterocyclic group, an aralkyl group having C_{6-10} aryl moiety and a C_{1-8} alkylene, or C_{1-8} alkyl having a 5- or 6-membered heterocyclic substituent;

each of R^3 and R^4 is independently hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

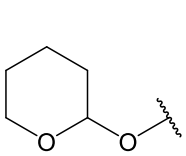
A is a 5-membered heterocycle which is pyrazole, thiophene, furan, isoxazole, isothiazole or pyrrole, in which the 5-membered heterocycle is unsubstituted or substituted with halogen,

hydroxyl, nitro, amino, C_{1-8} alkyl, 3- to 7-membered cycloalkyl group, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and C_{1-8} alkylene moiety, or C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

B is a bond or C_{1-8} alkylene which is unsubstituted or substituted with C_{1-8} alkyl, 3- to 7-membered cycloalkyl, C_{1-8} alkoxy or a halogen substituent, optionally wherein the C_{1-8} alkylene has a double or triple bond;

r is 0, 1, 2, or 3;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,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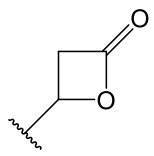
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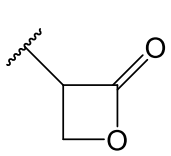
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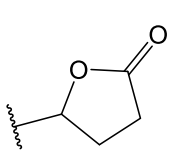
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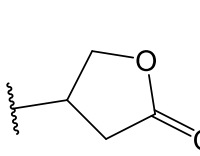
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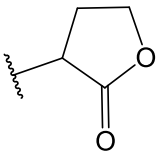
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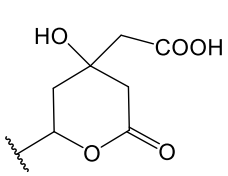
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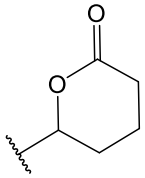
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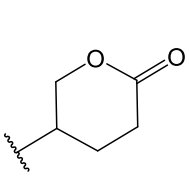
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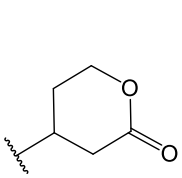
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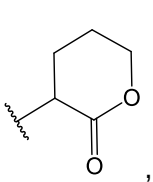
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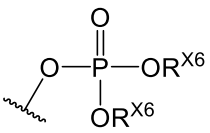
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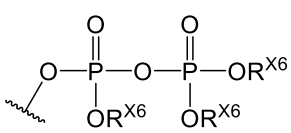
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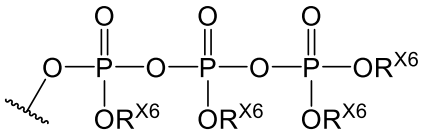
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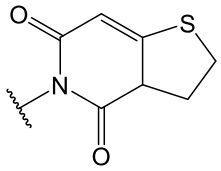
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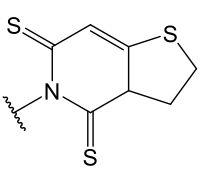
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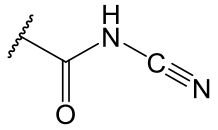
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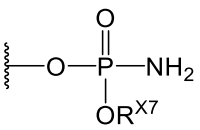
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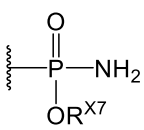
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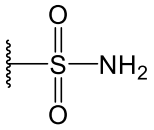
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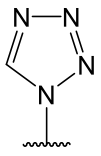
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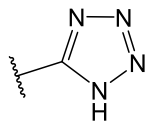
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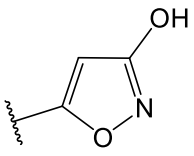
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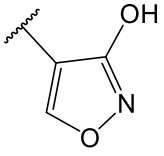
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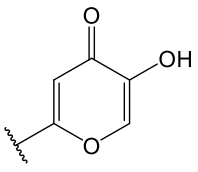
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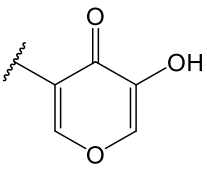
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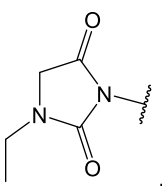
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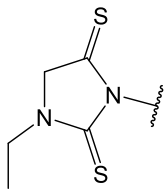
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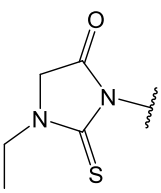
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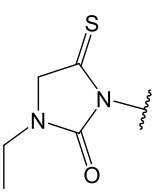
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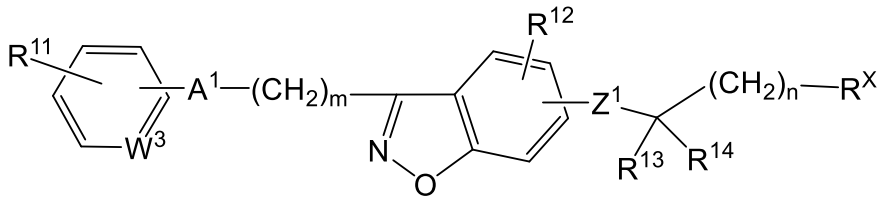
each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018j] In another aspect, the present disclosure provides a compound of Formula (N):



(N)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

W^3 is nitrogen or CH;

Z^1 is oxygen or sulfur;

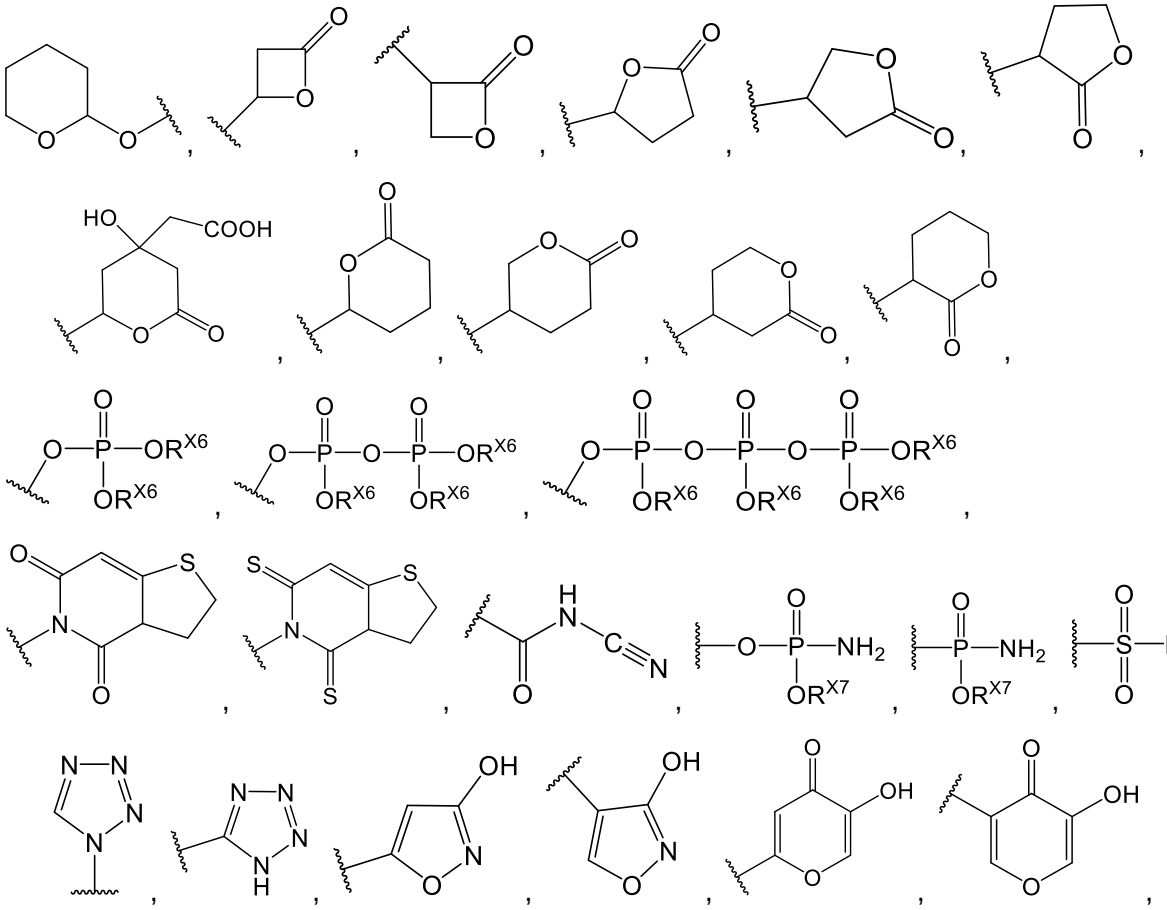
each of R^{11} and R^{12} is independently hydrogen, halogen, hydroxyl, nitro, amino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, or C_{1-8} haloalkoxy'

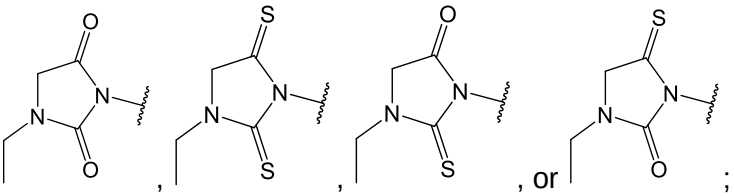
each of R^{13} and R^{14} is independently hydrogen or C_{1-8} alkyl;

A^1 is a 5-membered heterocycle which is pyrazole or thiophene, in which the 5-membered heterocycle is unsubstituted or substituted with halogen, hydroxyl, nitro, amino, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, or C_{1-8} haloalkoxy;

m is 2, 3, or 4;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



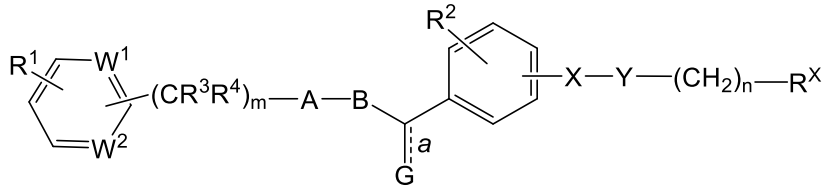


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018k] In another aspect, the present disclosure provides a compound of Formula (O):



(O)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of W^1 and W^2 independently is CH or nitrogen;

X is NR^5 or CR^6R^7; wherein R^5 is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkyl substituted with C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{1-8} alkyl substituted with C_{3-7} cycloalkyl, C 1-8 alkyl substituted with phenyl, C_{2-8} acyl, or C_{2-8} alkenyl, and each of R^6 and R^7 independently is hydrogen or C_{1-8} alkyl;

Y is $(CR^8R^9)_r$, wherein each of R^8 and R^9 independently is hydrogen or C_{1-8} alkyl, and r is 1, 2, 3, or 4; or

X and Y are combined to form $CR^{10}=CR^{11}$ or ethynylene, wherein each of R^{10} and R^{11} independently is hydrogen or C_{1-8} alkyl;

G, when bond *a* is present, is O, S or $CR^{12}R^{13}$, wherein each of R^{12} and R^{13} independently is hydrogen or C_{1-8} alkyl; G, when bond *a* is absent, is OH;

A is a five-membered heterocyclic ring which is thiazole, oxazole, imidazole, pyrazole, thiophene, furan, or pyrrole, wherein the heterocyclic ring is unsubstituted or substituted with C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, C_{2-8} acyl, C_{6-10} aryl, or a five-membered or six-membered heterocyclic group;

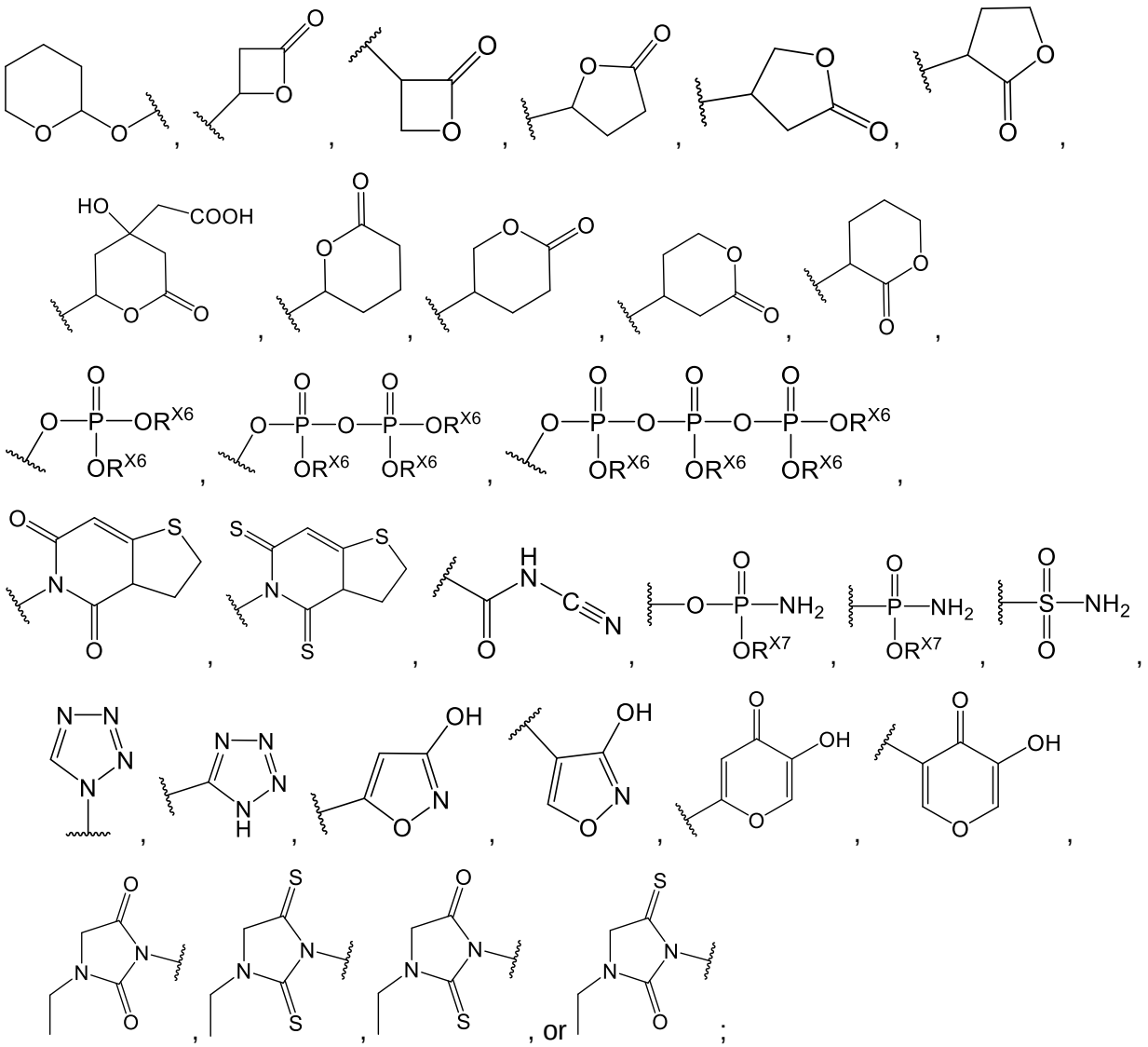
B is a C_{1-8} alkylene, C_{2-8} alkenylene or C_{2-8} alkynylene chain, wherein the chain is unsubstituted or substituted with C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-8} alkoxy, or halogen;

each of R^1 and R^2 independently is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, C_{2-8} acyl, C_{6-10} aryl, or a five-membered or six-membered heterocyclic group;

each of R^3 and R^4 independently is hydrogen or C_{1-8} alkyl;

m is 0, 1, 2, or 3;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

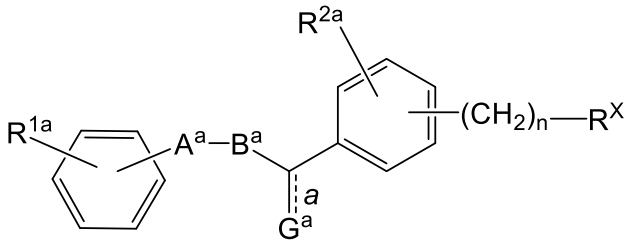


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018l] In another aspect, the present disclosure provides a compound of Formula (P):



(P)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

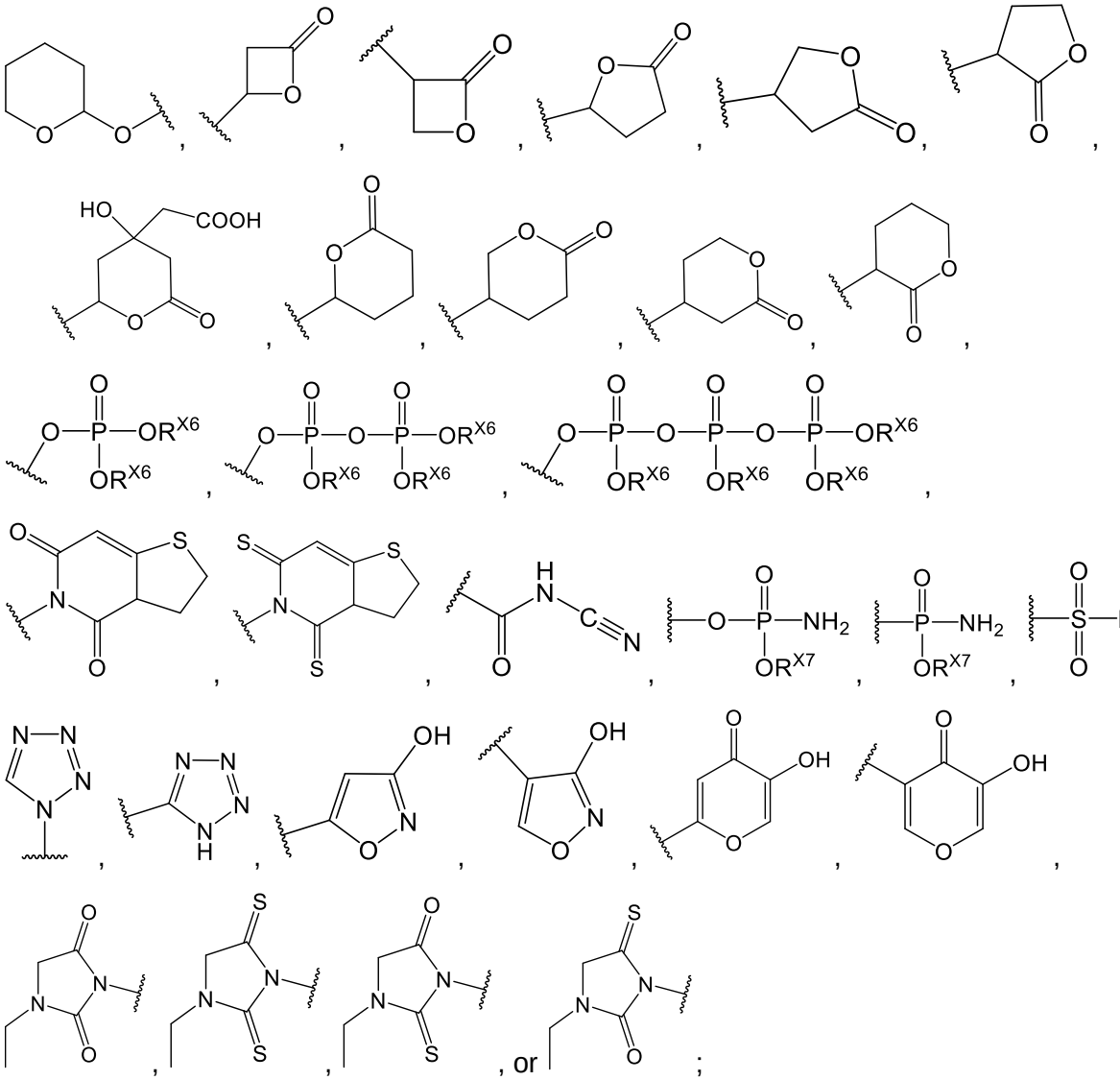
G^a, when bond a is present, is O, S or CH_2; G^a, when bond a is absent, is OH.

A^a is five-membered heterocyclic ring which is thiazole, oxazole, or thiophene, wherein the five-membered heterocyclic ring is unsubstituted or is substituted with C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, or C_{2-8} acyl;

B^a is a C_{1-8} alkylene or C_{2-8} alkenylene chain;

each of R^{1a} and R^{2a} independently is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, or C_{2-8} acyl;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

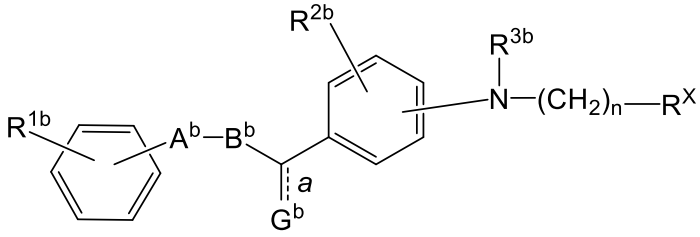


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018m] In another aspect, the present disclosure provides a compound of Formula (Q):



(Q)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

G^b, when bond *a* is present, is O, S or CH_2; G^b, when bond *a* is absent, is OH;

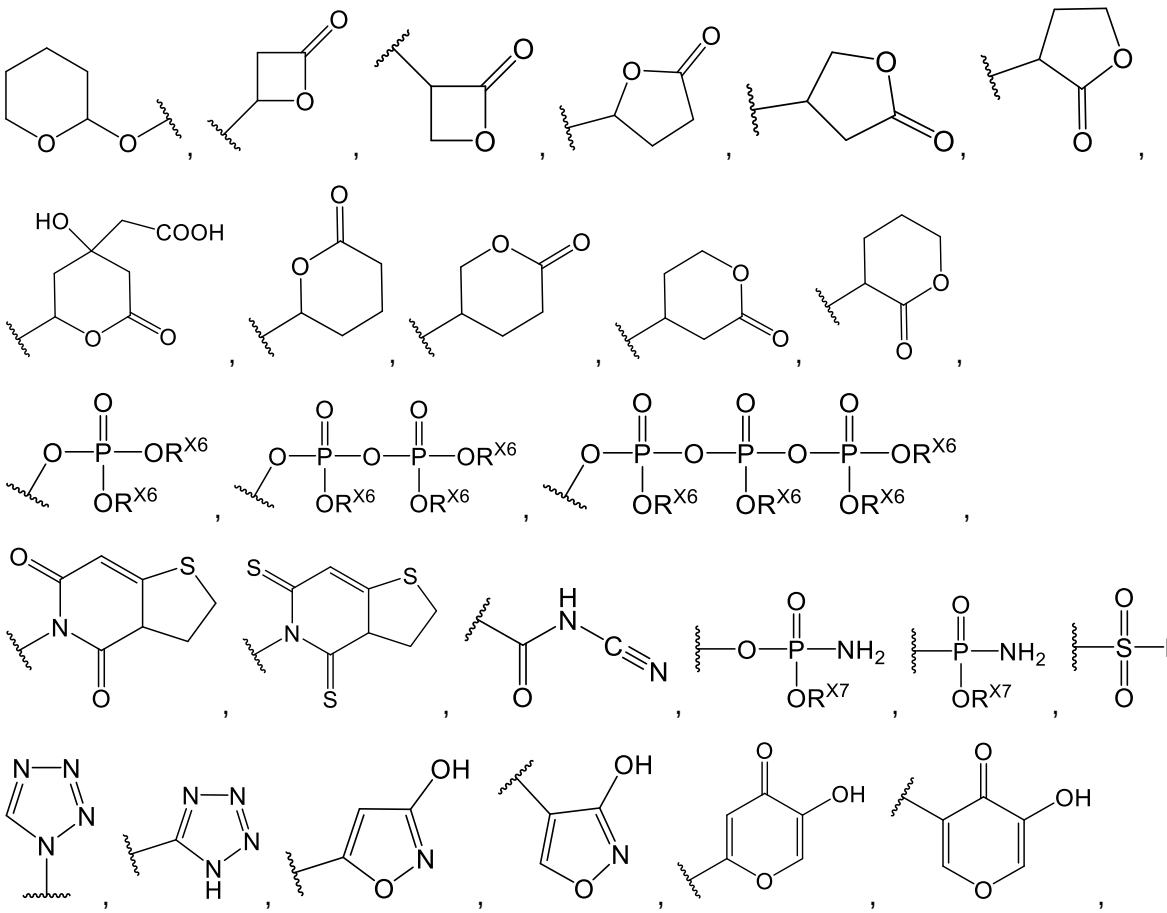
A^b is five-membered heterocyclic ring which is thiazole, oxazole, or thiophene, wherein the five-membered heterocyclic ring is unsubstituted or is substituted with C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, or C_{2-8} acyl;

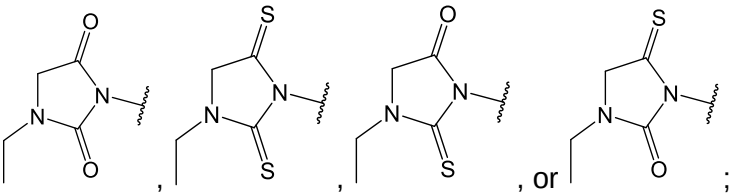
B^b is a C_{1-8} alkylene or C_{2-8} alkenylene chain;

each of R^{1b} and R^{2b} independently is hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, hydroxyl, nitro, or C_{2-8} acyl;

R^{3b} is hydrogen or C_{1-8} alkyl;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



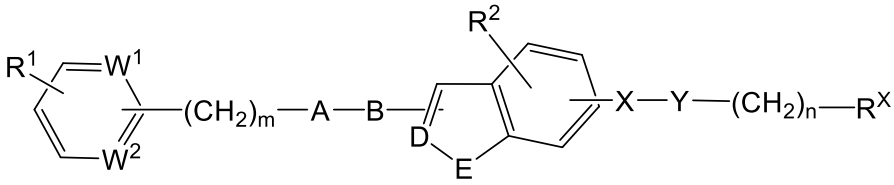


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018n] In another aspect, the present disclosure provides a compound of Formula (R):



(R)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

each of W^1 and W^2 is independently CH or N;

X is NR^3 or CR^4R^5, in which R^3 is C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkyl substituted with C_{1-8} alkoxy, C_{1-8} alkyl substituted with a 3-7 membered cycloalkyl, C_{1-8} alkyl substituted with a phenyl group, C_{2-8} acyl, or C_{2-8} alkenyl;

each of R^4 and R^5 is independently hydrogen or C_{1-8} alkyl;

Y is $(CR^6R^7)_r$, in which each of R^6 and R^7 is independently hydrogen or C_{1-8} alkyl and r is 1, 2, 3, or 4;

A is a 5 or 6-membered heterocyclic group which is thiazole, oxazole, imidazole, pyrazole, thiophene, furan, pyrrole, pyridine or pyrimidine, or a phenyl group, wherein the 5 or 6-membered heterocyclic group or phenyl group is unsubstituted or substituted with C_{1-8} alkyl, 3-7 membered cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxyl, C_{1-8} alkyl group substituted with a 3-7 membered cycloalkyl group, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, C_{6-10} aryl, a 5 or 6-membered heterocyclic group, aralkyl group comprising a C_{6-10} aryl group and a C_{1-8} alkyl group, or C_{1-8} alkyl group substituted with a 5 or 6-membered heterocyclic group;

B is a bond or C_{1-8} alkylene which is unsubstituted or substituted with C_{1-8} alkyl, a 3-7 membered cycloalkyl group, C_{1-8} alkoxy or a halogen, and which may have a double bond or triple bond when the carbon number of the alkylene chain is 2 or more;

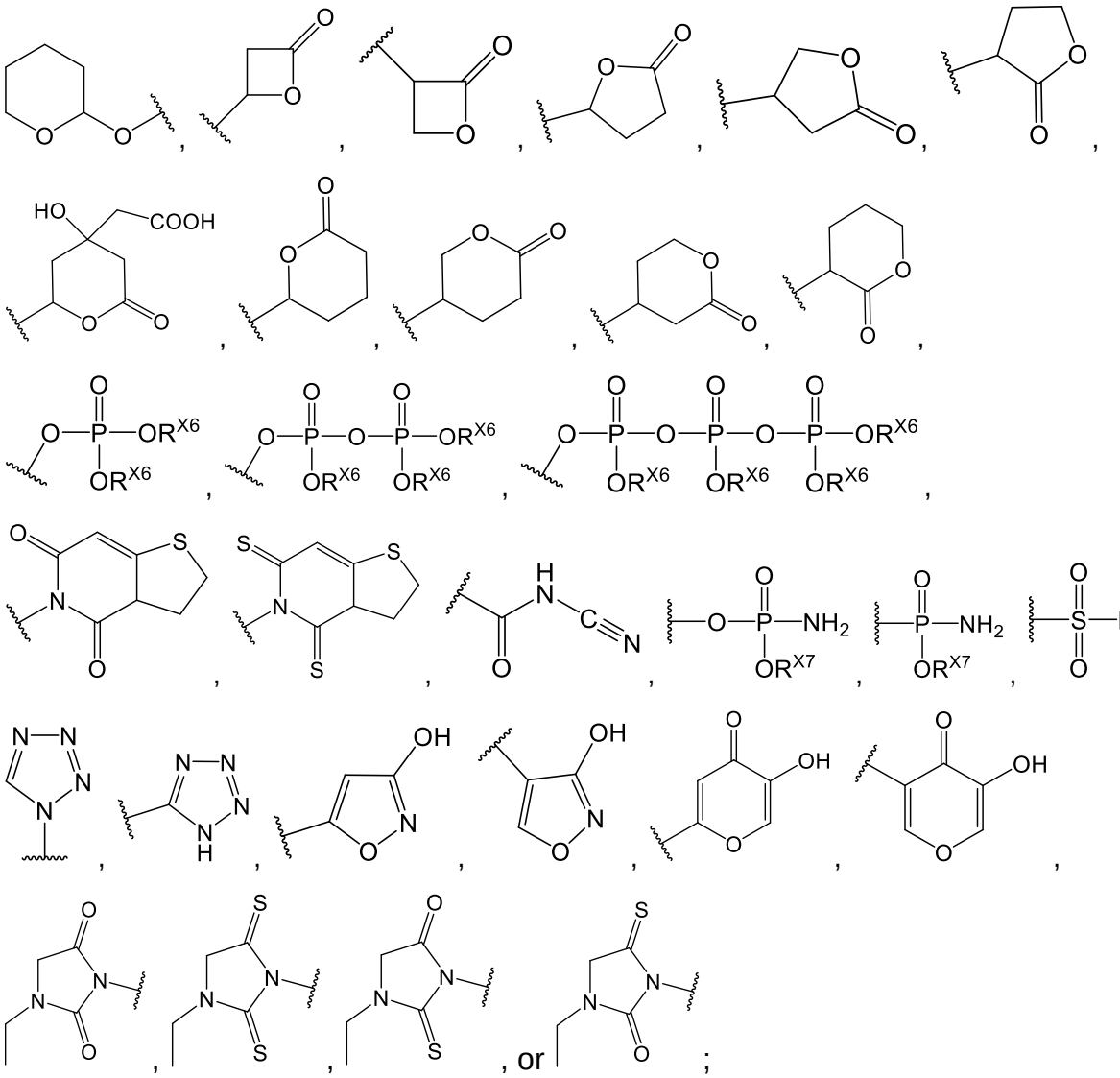
D is N or CH;

E is O or S;

each of R^1 and R^2 is independently H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, C_{1-8} haloalkyl, C_{1-8} haloalkoxy, nitro, C_{2-8} acyl, C_{6-10} aryl, or a 5 or 6-membered heterocyclic group;

m 0, 1, 2, or 3;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

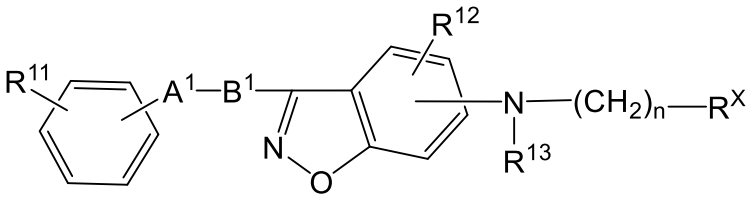


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018o] In another aspect, the present disclosure provides a compound of Formula (S):



(S)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

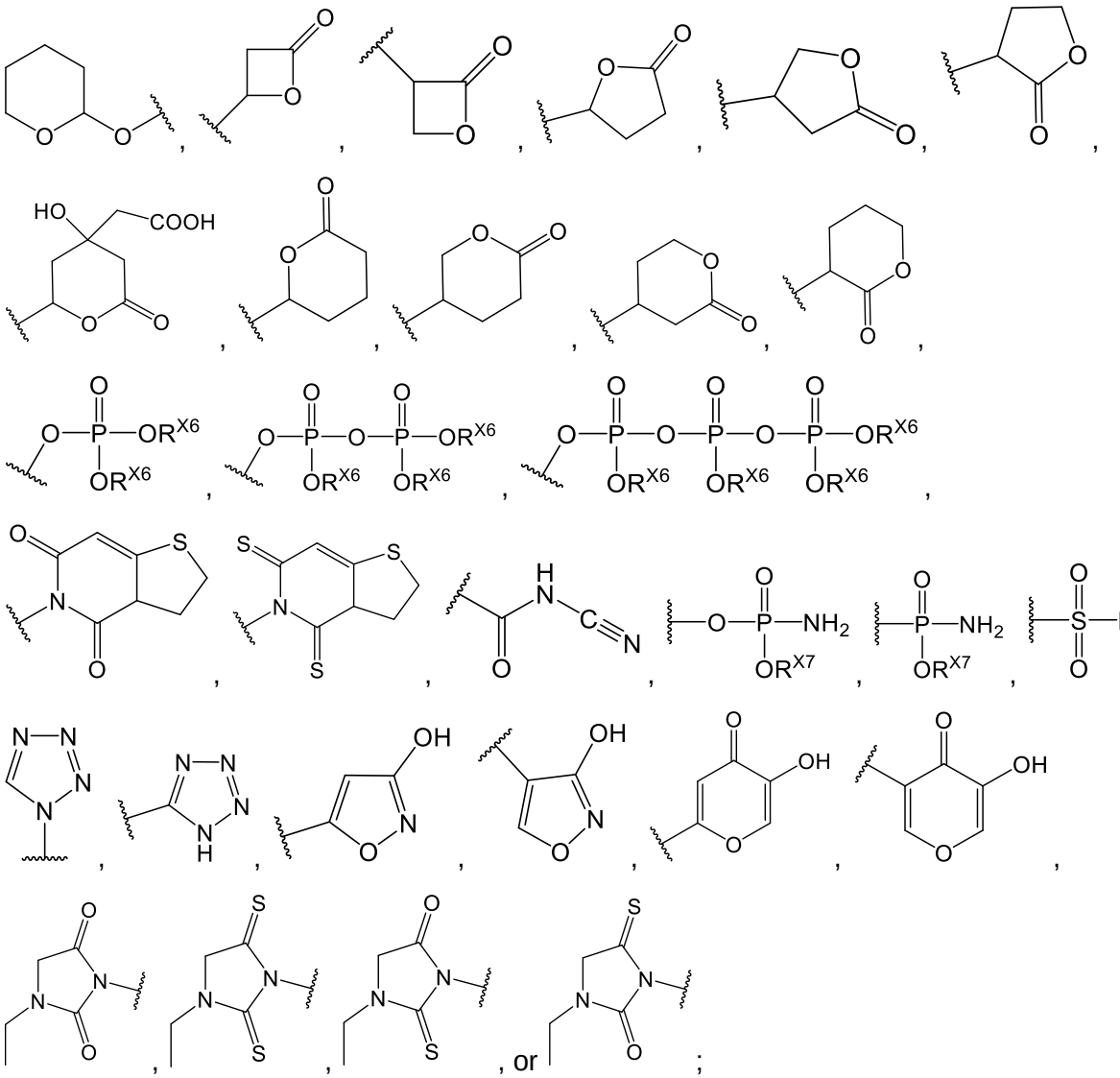
A^1 is a 5 or 6-membered heterocyclic group which is thiazole, oxazole, pyridine or pyrimidine, or a phenyl group, wherein the 5 or 6-membered heterocyclic group or phenyl group is unsubstituted or substituted with C_{1-8} alkyl or C_{1-8} haloalkyl;

B^1 is C_{2-4} alkylene;

each of R^{11} and R^{12} is independently H, C_{1-8} alkyl, halogen, or C_{1-8} haloalkyl;

R^{13} is C_{1-8} alkyl or C_{1-8} haloalkyl, optionally wherein the N to which R^{13} is attached is attached to the 6th position of benzisoxazole;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

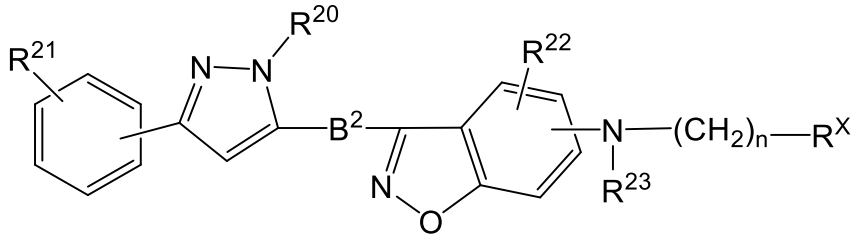


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018p] In another aspect, the present disclosure provides a compound of Formula (T):



(T)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

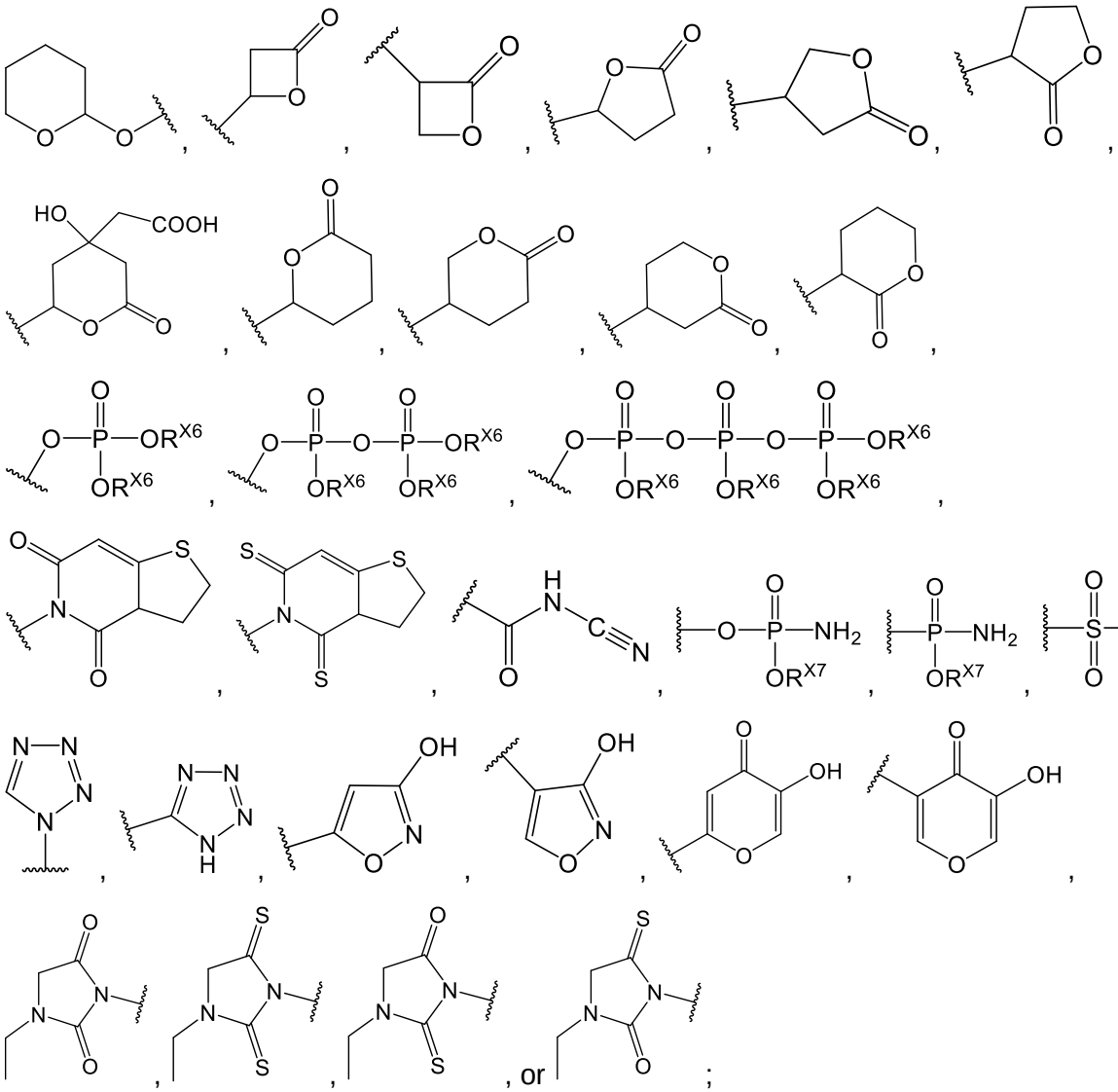
B^2 is C_{2-4} alkylene;

R^{20} is C_{1-8} alkyl;

each of R^{21} and R^{22} is independently H, C_{1-8} alkyl, halogen, or C_{1-8} haloalkyl;

R^{23} is C_{1-8} alkyl or C_{1-8} haloalkyl, optionally wherein the N to which R^{23} is attached is attached to the 6th position of benzisoxazole;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

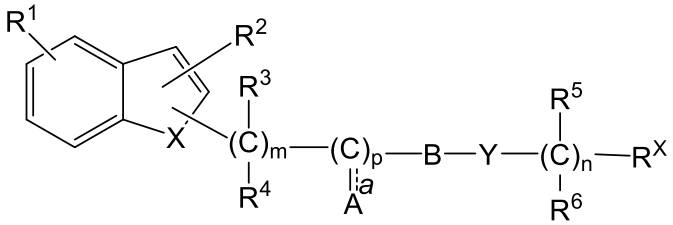


each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl; and

n is 0, 1, 2, 3, or 4.

[0018q] In another aspect, the present disclosure provides a compound of Formula (U):



(U)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^1 is hydrogen, halogen, hydroxyl, nitro, amino, cyano, carboxyl, C_{1-8} alkyl, C_{3-7} cycloalkyl, C2-C8 alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl group, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or a C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

R^2 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl group having a C_{1-8} alkoxy substituent, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

each of R^3, R^4, R^5 and R^6 independently is hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

X is oxygen, sulfur or NR^7; where R^7 is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, C_{2-8} acyl, or C_{2-8} alkenyl;

Y is oxygen, sulfur, NR^8 or a bond, where R^8 is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} acyl, or C_{2-8} alkenyl;

p is 0 or 1;

A, when bond *a* is present, is oxygen CH_2, N-NH_2 or N-OR^9, where R^9 is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} acyl, C_{2-8} alkenyl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety; A, when bond *a* is absent, is OH;

B is, in the case of p=1, a benzene ring having or not having a substituent which is halogen, hydroxyl, nitro, amino, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl group, or an aralkyl group having a C_{6-10} aryl moiety and a C1-C8 alkylene moiety of 1-8 carbon atoms, and, in the case of p=0, a condensed ring which is indole, benzofuran, benzisoxazole or 1,2-benzisothiazole, in which said condensed ring has or does not have a substituent which is

halogen, hydroxyl, nitro, amino, C_{1-8} alkyl group, C_{3-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl

having a C1-C8 alkoxy substituent, C_{1-8} haloalkoxy group, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

Y is bonded to the benzene ring of B;

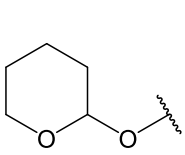
$(C(R^3)(R^4))_m$ is bonded to the condensed ring of B at its 3-position;

m is an integer of 1 to 4;

n is 0, 1, 2, 3, 4, or 5;

Y is a bond in the case of n=0;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,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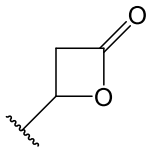
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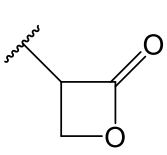
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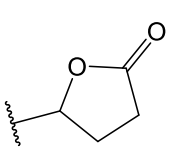
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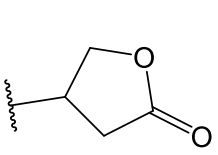
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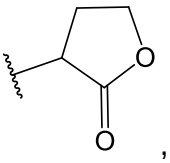
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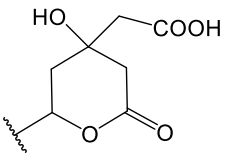
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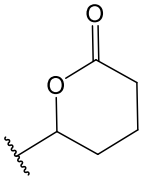
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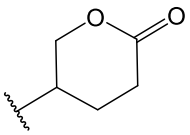
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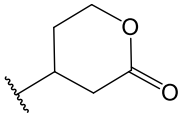
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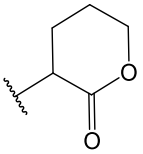
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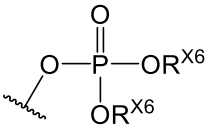
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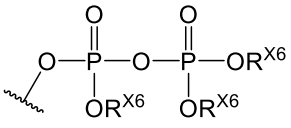
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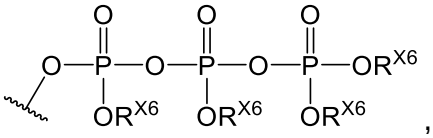
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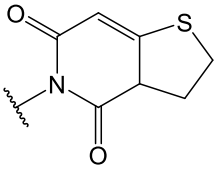
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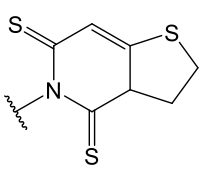
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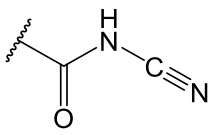
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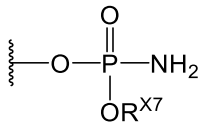
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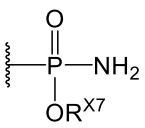
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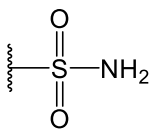
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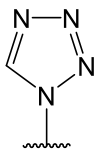
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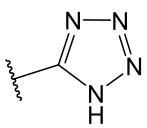
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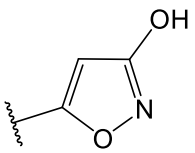
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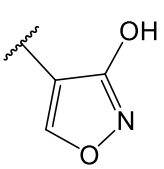
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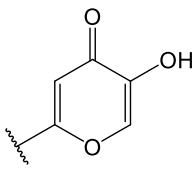
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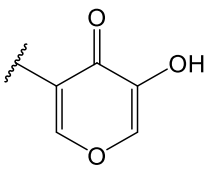
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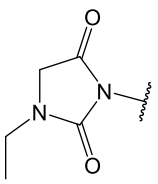
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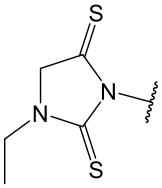
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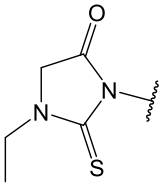
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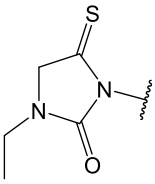
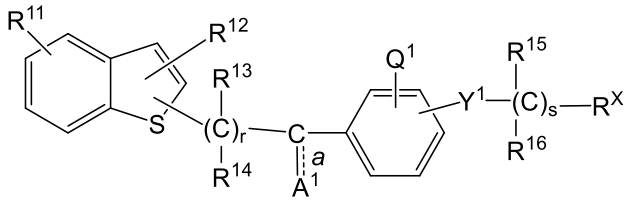

;

each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle; and each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl.

[0018r] In another aspect, the present disclosure provides a compound of Formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^{11} is hydrogen, halogen, hydroxyl, nitro, amino, cyano, carboxyl, C_{1-8} alkyl, C_{3-7} cycloalkyl, C2-C8 alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl group, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or a C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

R^{12} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl group having a C_{1-8} alkoxy substituent, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

each of R^{13}, R^{14}, R^{15} and R^{16} independently is hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

Y^1 is oxygen, sulfur, NR^{18} or a bond, where R^{18} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} acyl, or C_{2-8} alkenyl;

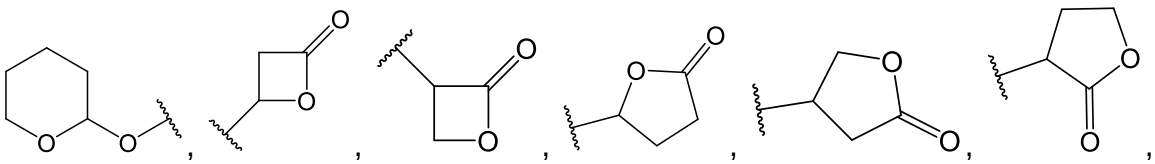
A^1, when bond *a* is present, is oxygen CH_2, $N\text{-}NH_2$ or $N\text{-}OR^{19}$, where R^{19} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} acyl, C_{2-8} alkenyl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety; A^1, when bond a is absent, is OH;

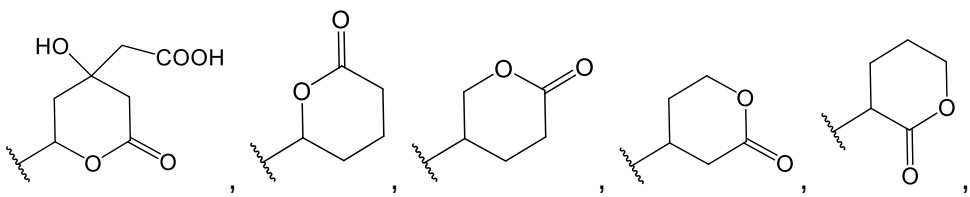
Q^1 is hydrogen, halogen, hydroxyl, nitro, amino, C_{1-8} alkyl group, C_{3-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

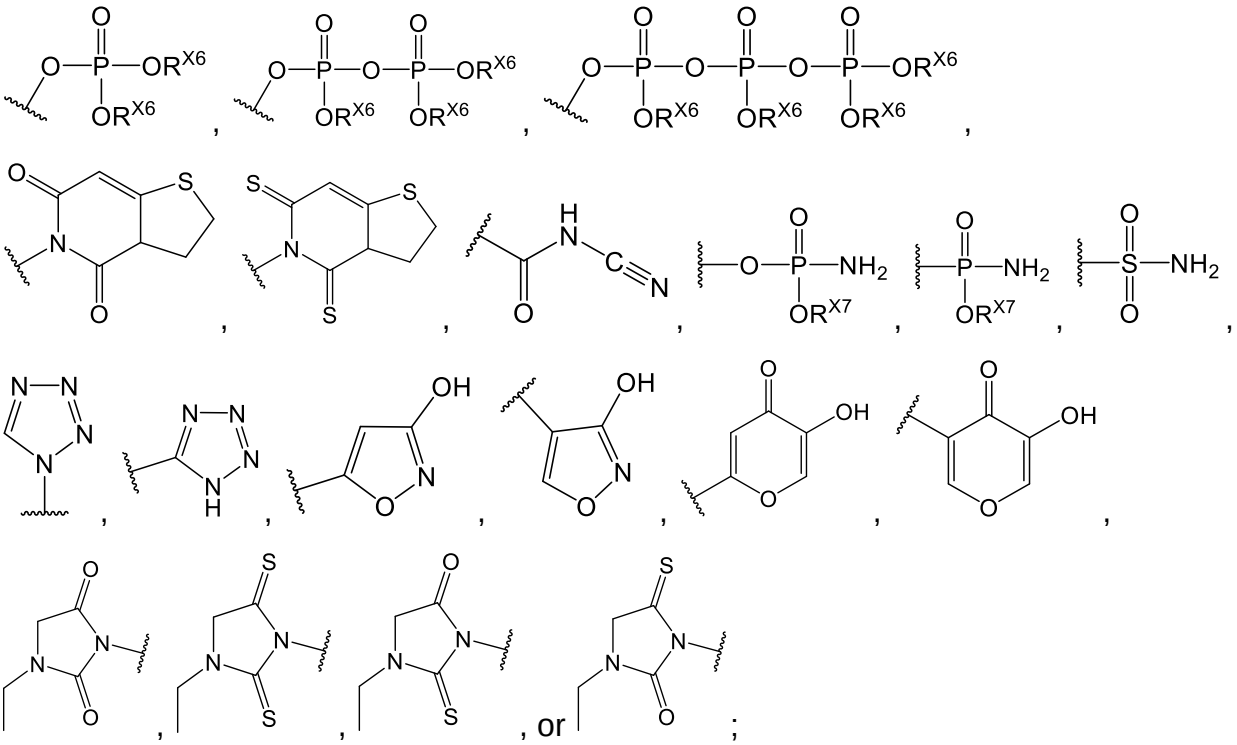
r is 1, 2, 3, or 4;

s is 1, 2, 3, 4, or 5;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



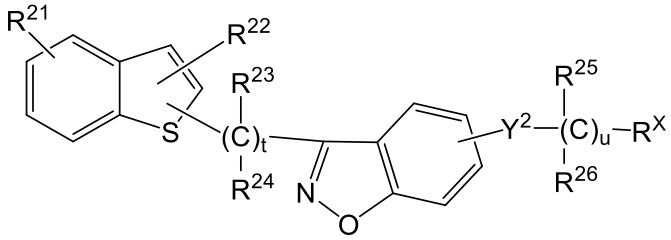




each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl.

[0018s] In another aspect, the present disclosure provides a compound of Formula (W):



(W)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^{21} is hydrogen, halogen, hydroxyl, nitro, amino, cyano, carboxyl, C_{1-8} alkyl, C_{3-7} cycloalkyl, C2-C8 alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl group, a 5- or 6-membered heterocyclic group, an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety, or a C_{1-8} alkyl group having a 5- or 6-membered heterocyclic substituent;

R^{22} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl group having a C_{1-8} alkoxy substituent, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

each of R^{23}, R^{24}, R^{25} and R^{26} independently is hydrogen, C_{1-8} alkyl, or C_{1-8} haloalkyl;

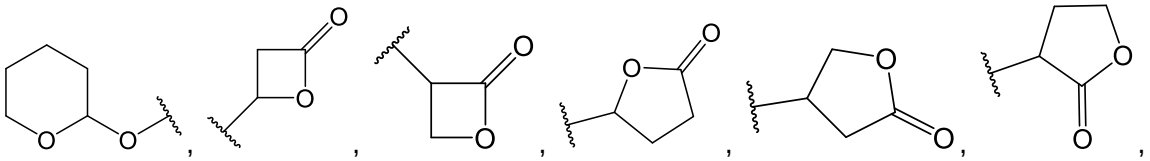
Y^2 is oxygen, sulfur, NR^{28} or a bond, where R^{28} is hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{2-8} acyl, or C_{2-8} alkenyl;

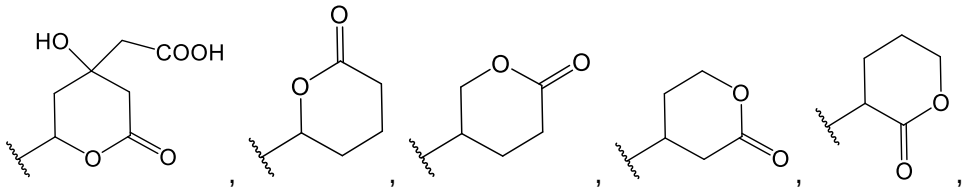
Q^2 is hydrogen, halogen, hydroxyl, nitro, amino, C_{1-8} alkyl group, C_{3-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkyl having a 3- to 7-membered cycloalkyl substituent, C_{1-8} haloalkyl, C_{1-8} alkyl having a C_{1-8} alkoxy substituent, C_{1-8} haloalkoxy, C_{2-8} acyl, C_{6-10} aryl, or an aralkyl group having a C_{6-10} aryl moiety and a C_{1-8} alkylene moiety;

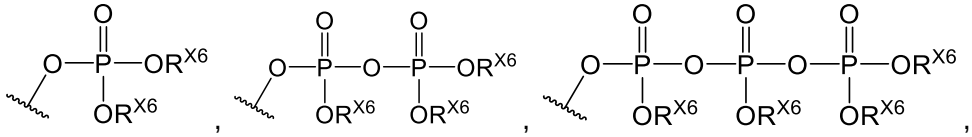
t is 1, 2, 3, or 4;

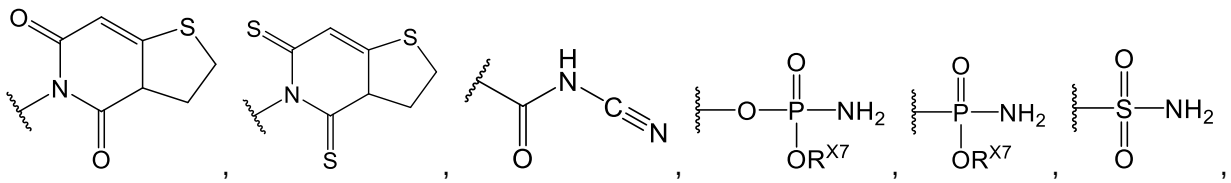
u is 1, 2, 3, 4, or 5;

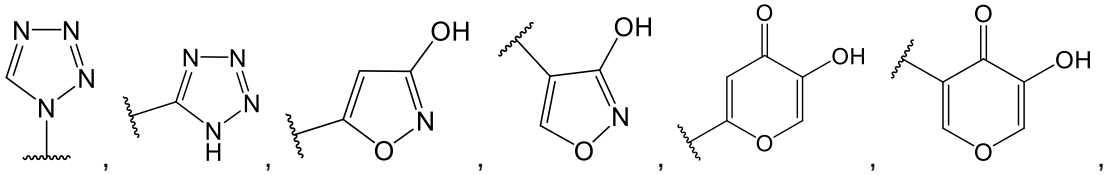
R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

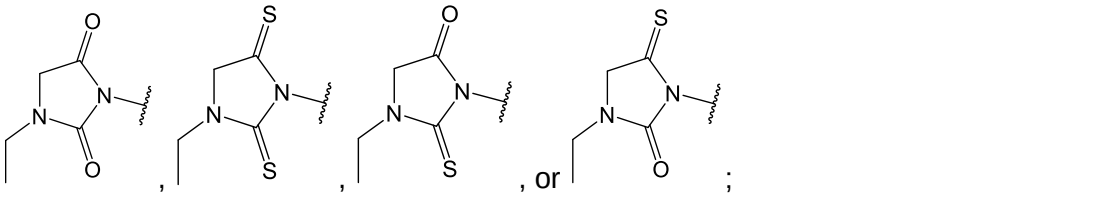








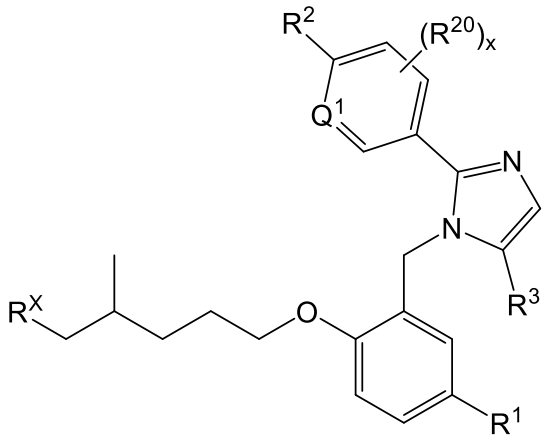




each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle;

each R^{X6} and R^{X7} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0018t] In another aspect, the present disclosure provides a compound of Formula (X):



(X)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{3-6} cycloalkyl;

Q^1 is CH or N;

R^2 is hydrogen, halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $S(C_{1-4}$ alkyl), $SO_2(C_{1-4}$-alkyl), 5- or 6-membered heterocycle, aryl, 5-membered heteroaryl, $C{\equiv}C\text{-}R^{2A}$, $O(CH_2)_mR^{2B}$, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, or $C(O)(C_{1-4}$ alkyl), wherein aryl and heteroaryl are unsubstituted or substituted with halogen, OH, CN, C_{1-4} alkyl, formyl, acetyl, acetoxy, or carboxy, and wherein m is 1, 2, or 3;

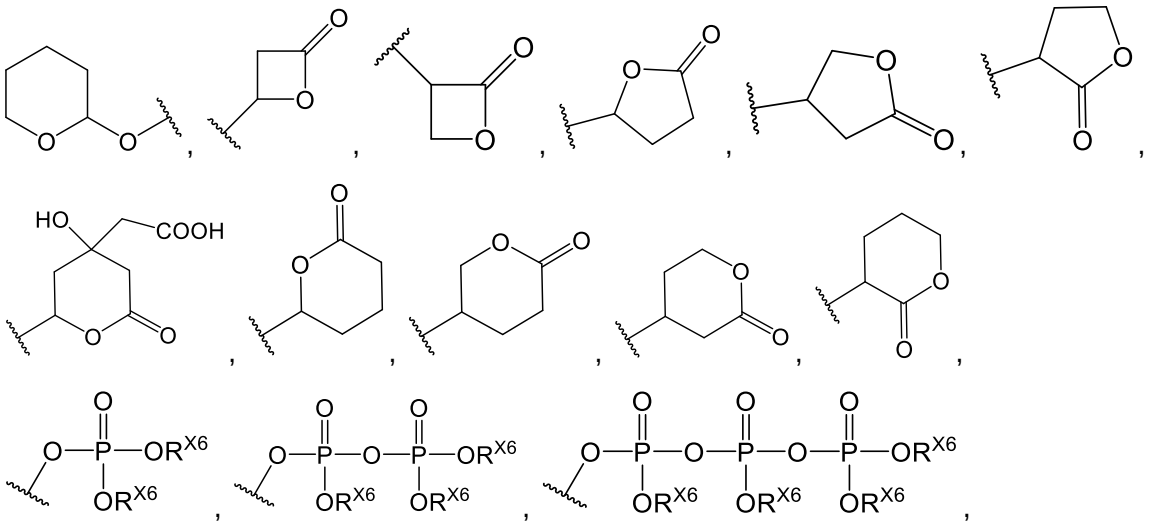
x is 1 or 2;

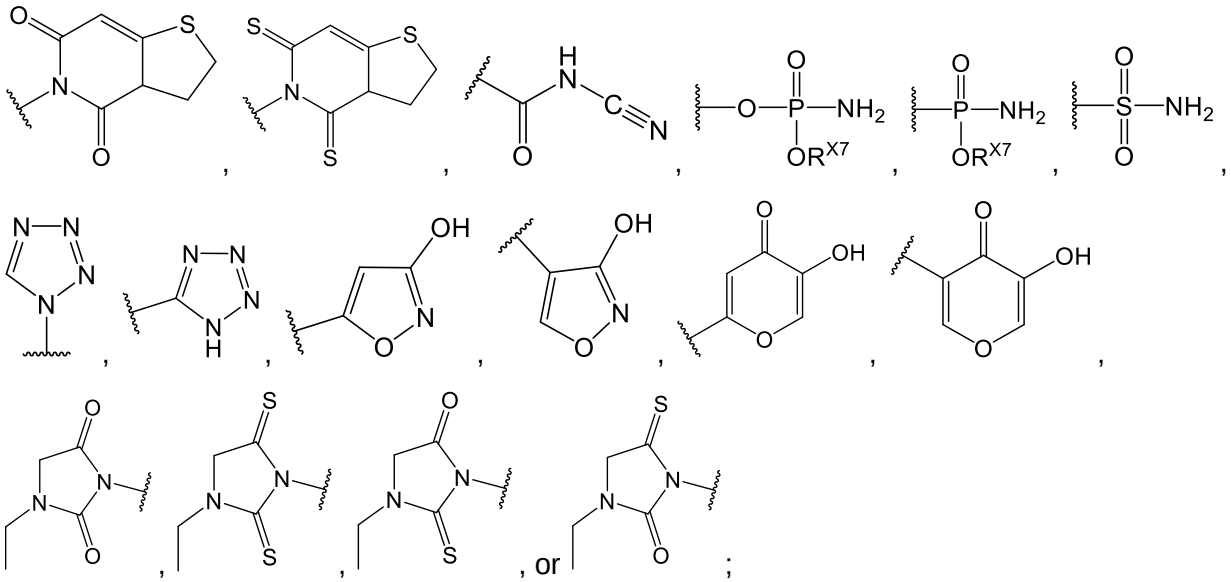
R^{2A} and R^{2B} are each independently C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl;

each R^{20} is independently hydrogen, halogen, C_{1-4} alkyl, CN, or C_{1-4} alkoxy;

R^3 is CH_3 or CD_3;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,

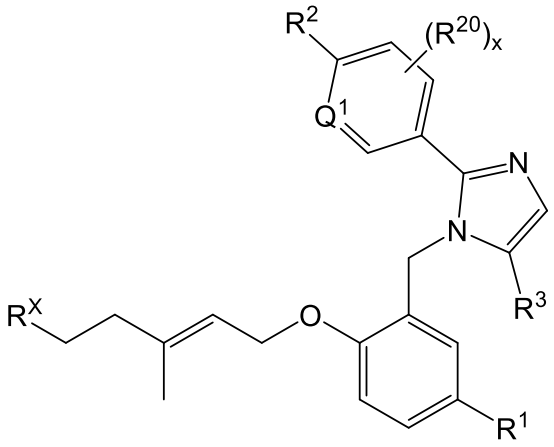




each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle; and

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl.

[0018u] In another aspect, the present disclosure provides a compound of Formula (Y):



(Y)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{3-6} cycloalkyl;

Q^1 is CH or N;

R^2 is hydrogen, halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $S(C_{1-4}$ alkyl), $SO_2(C_{1-4}$-alkyl), 5- or 6-membered heterocycle, aryl, 5-membered heteroaryl, $C{\equiv}C\text{-}R^{2A}$, $O(CH_2)_mR^{2B}$, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, or $C(O)(C_{1-4}$ alkyl), wherein aryl and heteroaryl are unsubstituted or substituted with halogen, OH, CN, C_{1-4} alkyl, formyl, acetyl, acetoxy, or carboxy, and wherein m is 1, 2, or 3;

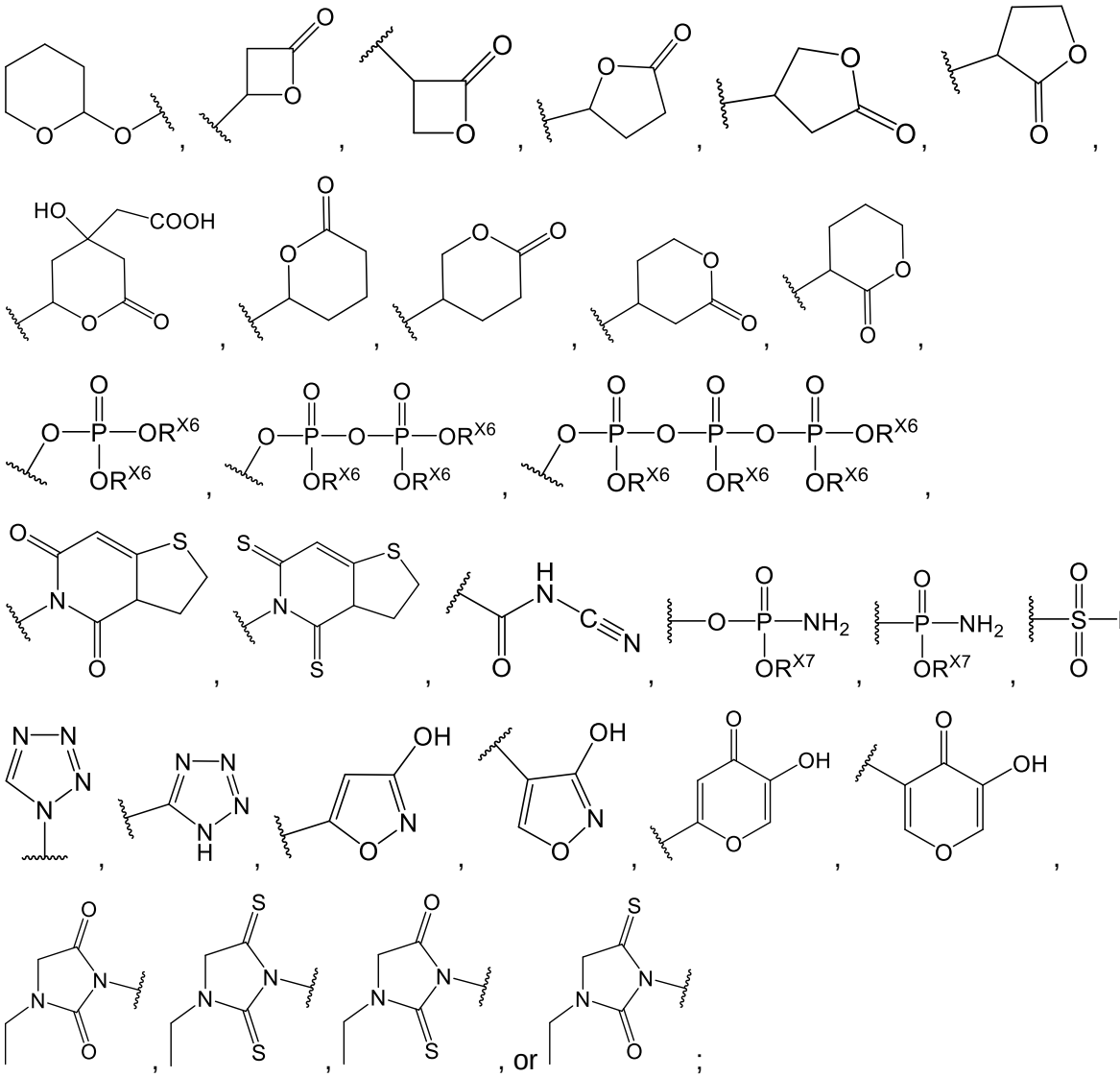
x is 1 or 2;

R^{2A} and R^{2B} are each independently C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl;

each R^{20} is independently hydrogen, halogen, C_{1-4} alkyl, CN, or C_{1-4} alkoxy;

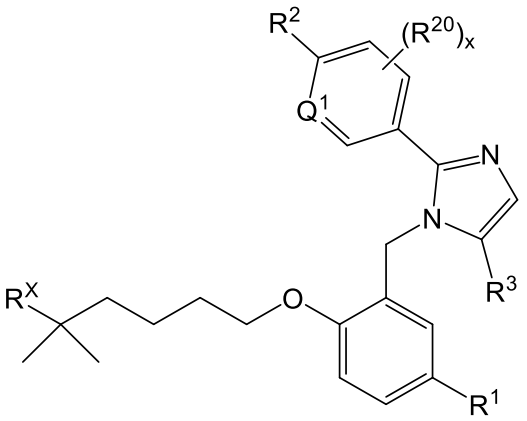
R^3 is CH_3 or CD_3;

R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle; and each R^{X6} and R^{X7} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0018v] In another aspect, the present disclosure provides a compound of Formula (Z):



(Z)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

R^1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{3-6} cycloalkyl;

Q^1 is CH or N;

R^2 is hydrogen, halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, S(C_{1-4} alkyl), SO_2(C_{1-4}-alkyl), 5- or 6-membered heterocycle, aryl, 5-membered heteroaryl, C≡C-R^{2A}, $O(CH_2)_mR^{2B}$, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, or C(O)(C_{1-4} alkyl), wherein aryl and heteroaryl are unsubstituted or substituted with halogen, OH, CN, C_{1-4} alkyl, formyl, acetyl, acetoxy, or carboxy, and wherein m is 1, 2, or 3;

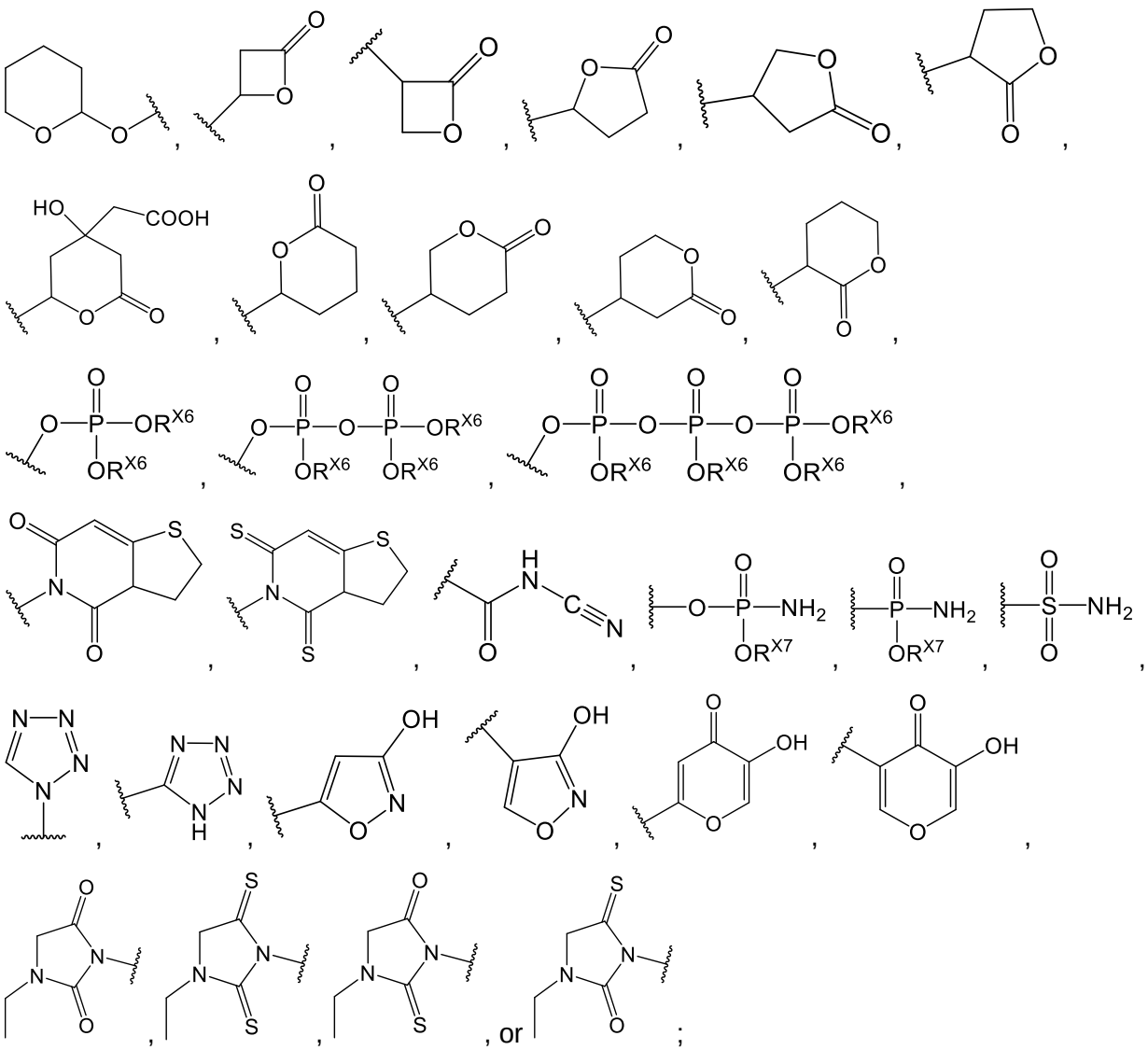
x is 1 or 2;

R^{2A} and R^{2B} are each independently C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl;

each R^{20} is independently hydrogen, halogen, C_{1-4} alkyl, CN, or C_{1-4} alkoxy;

R^3 is CH_3 or CD_3;

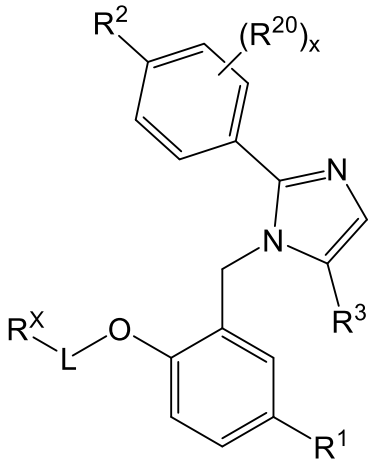
R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,



each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle; and

each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl.

[0018w] In another aspect, the present disclosure provides a compound of Formula (AA):



(AA)

or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof, wherein:

L is $(CH_2)_5$, which is unsubstituted or substituted by one methyl group;

R^1 is hydrogen, halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, CN, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{3-6} cycloalkyl;

R^2 is hydrogen, halogen, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $S(C_{1-4}$ alkyl), $SO_2(C_{1-4}$-alkyl), 5- or 6-membered heterocycle, aryl, 5-membered heteroaryl, $C{\equiv}C\text{-}R^{2A}$, $O(CH_2)_mR^{2B}$, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, or $C(O)(C_{1-4}$ alkyl), wherein aryl and heteroaryl are unsubstituted or substituted with halogen, OH, CN, C_{1-4} alkyl, formyl, acetyl, acetoxy, or carboxy, and wherein m is 1, 2, or 3;

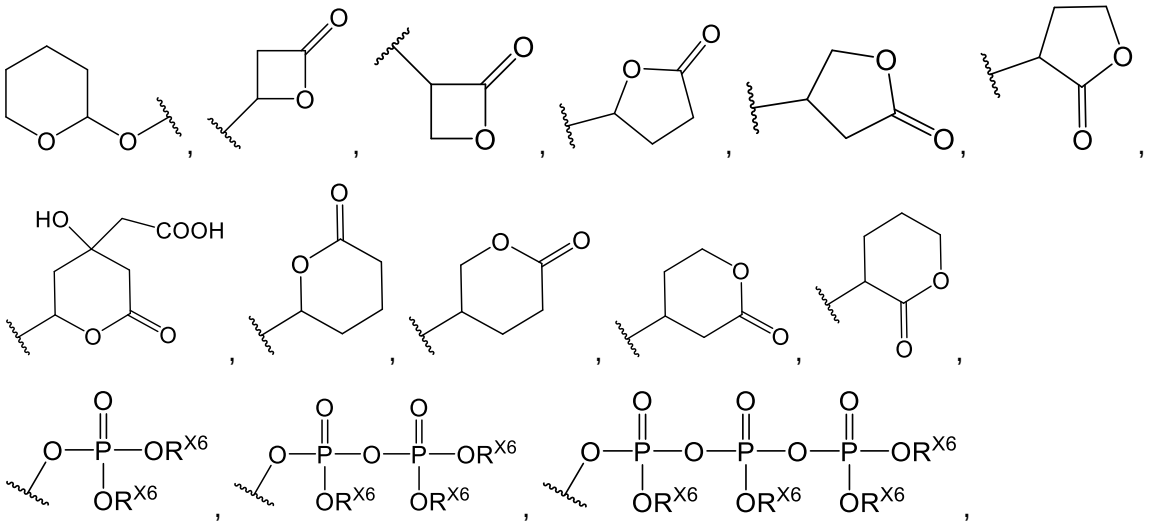
x is 0 or 1;

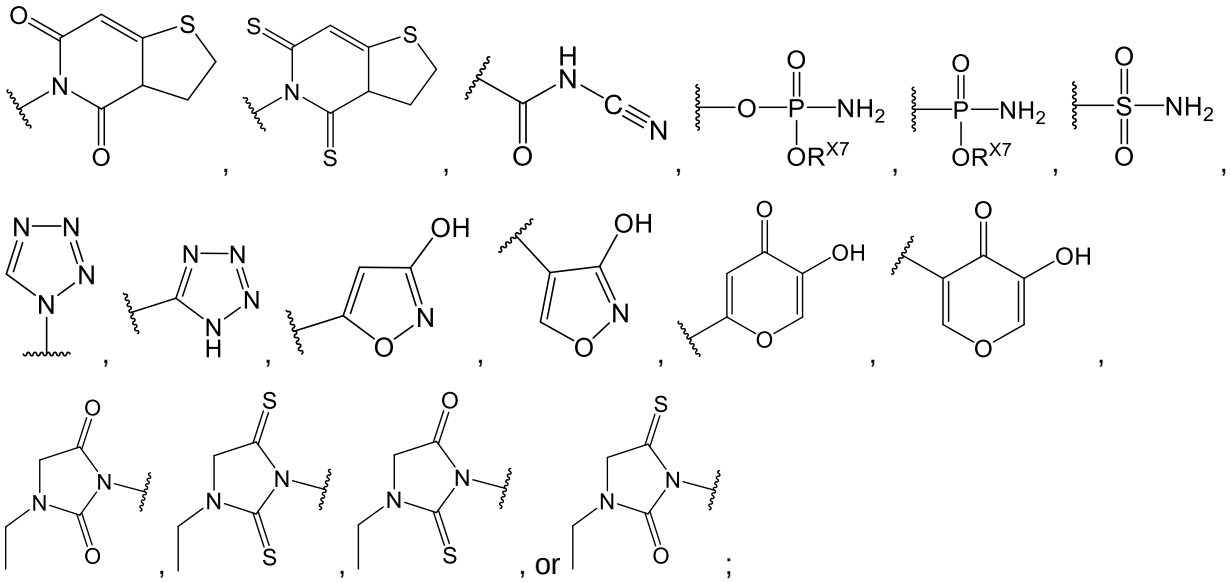
R^{2A} and R^{2B} are each independently C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-6} cycloalkyl;

R^3 is C_{1-4} haloalkyl, NO_2, CN, halogen, or $C(O)O(C_{1-4}$ alkyl);

R^{20} is hydrogen, halogen, C_{1-4} alkyl, CN, or C_{1-4} alkoxy;

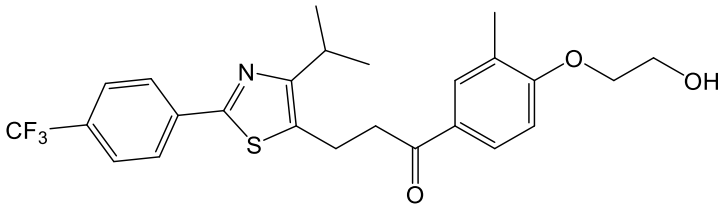
R^X is CH_2OH, COH, $COOCH_2CONR^{X4}R^{X5}$, SO_3H,





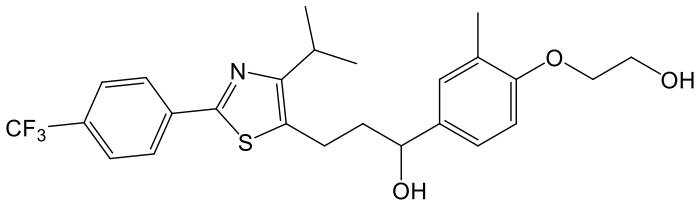
each R^{X4} and R^{X5} is independently alkyl, aryl, or heteroaryl; or alternatively, R^{X4} and R^{X5} together with the carbon atom to which R^{X4} and R^{X5} are attached form a heterocycle; and each R^{X6} and R^{X7} is independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, or $C_{2–6}$ alkynyl.

[0019] The present disclosure further provides a compound having the structure



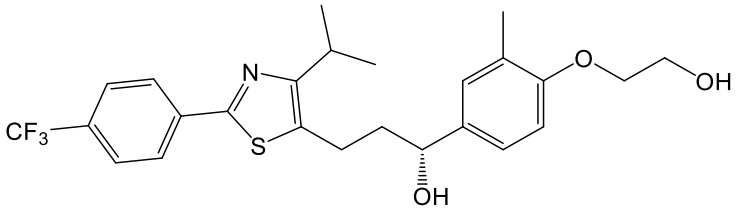
("Compound IV") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

[0020] The present disclosure further provides a compound having the structure



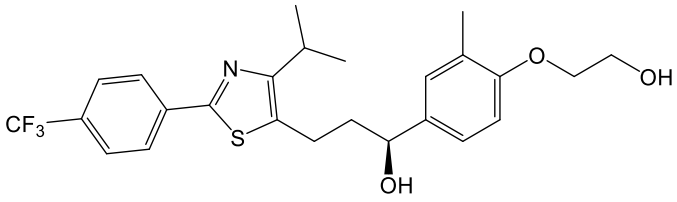
("Compound V") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

[0021] The present disclosure further provides a compound having the structure



("Compound Va") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

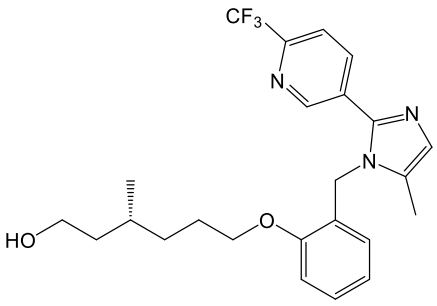
[0022] The present disclosure further provides a compound having the structure



("Compound Vb") and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

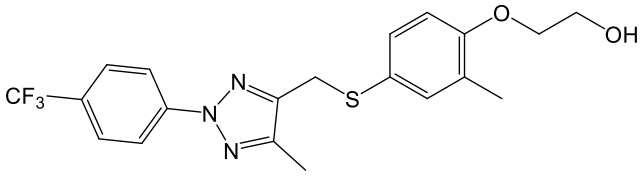
[0023] In further examples, the disclosure provides compounds of Formula (D)-(H) and (J)-(AA), *e.g.*, as described in Section 5.2 (including subparts) and pharmaceutically acceptable salts, solvates, esters, amides, and prodrugs thereof.

[0024] In another aspect, the present disclosure provides a compound having the structure



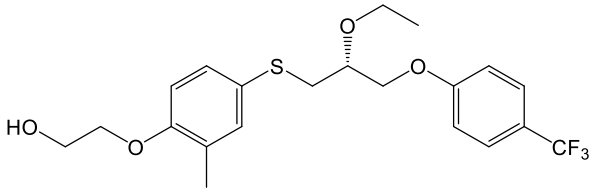
("Compound VI") or pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof.

[0025] In another aspect, the present disclosure provides a compound having the structure



("Compound VII") or pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof.

[0026] In another aspect, the present disclosure provides a compound having the structure

[0027] 

("Compound VIII") or pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof.

[0028] Each compound of Formula (A)-(H) and (J)-(AA), each compound of Compounds I, II, III, IV, V, Va, Vb, VI, VII, and VIII, and each compound described in Sections 5-7 (including their subparts), or a pharmaceutically acceptable salt, solvate, ester, amide, and prodrug thereof is a

"compound of the invention". Exemplary features of compounds of the invention are described in Section 5.2 and specific embodiments 1 to 50 in Section 7.1 and 1 to 209 in Section 7.2, *infra*.

[0029] There are also provided compositions comprising i) an effective amount of a compound of the invention and ii) a pharmaceutically acceptable carrier or vehicle (each composition being a "composition of the invention"). Exemplary features of pharmaceutical compositions of the disclosure are described in Section 5.3 and specific embodiments 51 to 54 in Section 7.1 and 210 to 213 in Section 7.2, *infra*.

[0029a] In another aspect, the present disclosure provides a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt, solvate, ester, amide, or prodrug of the compound as defined herein and a pharmaceutically acceptable carrier or vehicle.

[0029b] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing a liver disorder, dyslipidemia, dyslipoproteinemia, a renal disease, a disorder of glucose metabolism, a disorder of lipid metabolism, a disorder of glucid metabolism, a cardiovascular disease, a vascular disease, a metabolic syndrome, a complication associated with metabolic syndrome, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, diabetic nephropathy, diabetic retinopathy, atherosclerosis, pancreatitis, a cerebrovascular disease, a disorder related to neovascularization, hypertension, cancer, inflammation, an inflammatory disease, a neurodegenerative disease, an autoimmune disease, a neoplastic disease, muscle atrophy, cholestasis, mitochondrial dysfunction, an ocular disease, a lysosomal storage disease, a kidney disease, or impotence.

[0029c] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, or dyslipidemia.

[0029d] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing an abnormally high concentration in a subject's blood plasma or blood serum of high low-density lipoprotein (LDL), apolipoprotein B (apo B), lipoprotein(a) (Lp(a)), apolipoprotein (a), or very low-density lipoprotein (VLDL).

[0029e] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing an abnormally low concentration in a subject's blood plasma or blood serum of high-density lipoprotein (HDL).

[0029f] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or

preventing an abnormally reduced or deficient lipoprotein lipase concentration or activity in a subject’s blood plasma or blood serum.

[0029g] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing hypoalphalipoproteinemia, a lipoprotein abnormality associated with diabetes, a lipoprotein abnormality associated with obesity, a lipoprotein abnormality associated with Alzheimer's Disease, or familial combined hyperlipidemia.

[0029h] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in reducing in a subject’s blood plasma or blood serum an abnormally high concentration of triglyceride, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol, (non-HDL-C), lipoprotein(a) (Lp(a)), apolipoprotein B, HDL/(VLDL+LDL) ratio, apolipoprotein C-II or apolipoprotein C-III.

[0029i] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in elevating in a subject’s blood plasma or blood serum an abnormally low concentration of a high-density lipoprotein (HDL)-associated protein, HDL-cholesterol, apolipoprotein A-I, or apolipoprotein E.

[0029j] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in promoting clearance of triglyceride from a subject’s blood plasma or blood serum.

[0029k] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in increasing abnormally low glucose metabolism or lipid metabolism in a subject.

[0029l] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in treating or preventing a symptom of inflammation, systemic lupus erythematosus, lupus nephritis, or arthritis.

[0029m] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in reducing the fat content of meat in livestock.

[0029n] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in reducing cholesterol content of a fowl egg.

[0029o] In another aspect, the present disclosure provides a compound as defined herein or a pharmaceutically acceptable salt, solvate, ester, amide, or prodrug thereof for use in a method for treating a subject with acute kidney injury (AKI) or at risk for AKI, comprising administering to the subject (i) an effective amount of the compound or the pharmaceutically acceptable salt, solvate, ester, amide, or prodrug of the compound.

[0030] The present disclosure further provides methods for treating or preventing a liver disorder, dyslipidemia, dyslipoproteinemia, a renal disease, a disorder of glucose metabolism, a disorder of lipid metabolism, a disorder of glucid metabolism, a cardiovascular disease, a vascular disease, a metabolic syndrome, a complication associated with metabolic syndrome, a PPAR-associated disorder, septicemia, a thrombotic disorder, obesity, diabetic nephropathy, diabetic retinopathy, atherosclerosis, pancreatitis, a cerebrovascular disease, a disorder related to neovascularization, hypertension, cancer, inflammation, an inflammatory disease, a neurodegenerative disease, an autoimmune disease, a neoplastic disease, muscle atrophy, cholestasis, mitochondrial dysfunction, an ocular disease, a lysosomal storage disease, a kidney disease (*e.g.*, acute kidney injury), or impotence, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0031] The present disclosure further provides methods for treating or preventing hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, or dyslipidemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0032] The present disclosure further provides methods for treating a subject having or preventing a subject from having an abnormally high concentration in a subject's blood plasma or blood serum of high low-density lipoprotein (LDL), apolipoprotein B (apo B), lipoprotein(a) (Lp(a)), apolipoprotein (a), or very low-density lipoprotein (VLDL), comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0033] The present disclosure further provides methods for treating a subject having or preventing a subject from having an abnormally low concentration in a subject's blood plasma or blood serum of high-density lipoprotein (HDL), comprising administering to a subject in need thereof an effective amount of the compound of the invention or the composition of the invention.

[0034] The present disclosure further provides methods for treating a subject having or preventing a subject from having an abnormally reduced or deficient lipoprotein lipase concentration or activity

in a subject's blood plasma or blood serum, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0035] The present disclosure provides methods for treating or preventing hypoalphalipoproteinemia, a lipoprotein abnormality associated with diabetes, a lipoprotein abnormality associated with obesity, a lipoprotein abnormality associated with Alzheimer's Disease, or familial combined hyperlipidemia, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0036] The present disclosure further provides methods for reducing in a subject's blood plasma or blood serum an abnormally high concentration of triglycerides, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol, (non-HDL-C), lipoprotein(a) (Lp(a)), apolipoprotein B, HDL/(VLDL+LDL) ratio, apolipoprotein C-II or apolipoprotein C-III, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0037] The present disclosure further provides methods for elevating in a subject's blood plasma or blood serum an abnormally low concentration of a high-density lipoprotein (HDL) associated protein, HDL-cholesterol, apolipoprotein A-I, or apolipoprotein E, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0038] The present disclosure further provides methods for promoting clearance of triglycerides from a subject's blood plasma or blood serum, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0039] The present disclosure further provides methods for increasing abnormally low glucose metabolism or increasing abnormally low lipid metabolism in a subject, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0040] The present disclosure further provides methods for treating or preventing one or more symptoms of inflammation, systemic lupus erythematosus, lupus nephritis, or arthritis, comprising administering to a subject in need thereof an effective amount of a compound of the invention or a composition of the invention.

[0041] The present disclosure further provides methods for reducing the fat content of meat in livestock, comprising administering to livestock an effective amount of a compound of the invention or a composition of the invention.

[0042] The present disclosure further provides methods for reducing cholesterol content of a fowl egg, comprising administering to a fowl species an effective amount of a compound of the invention or a composition of the invention.