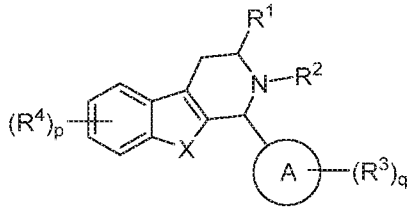
What is claimed is:

1. A compound of formula (I):



(I)

or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, wherein:

ring A is C_4-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is NR^5, O or S;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, -CN, -OH, $-C(O)OR^6$, $-C(O)N(R^7)_2$, $-OC(O)R^6$, $-S(O)_2R^8$, $-S(O)_2N(R^7)_2$, $-S(O)N(R^7)_2$, $-S(O)R^8$, $-NH_2$, $-NHR^8$, $-N(R^8)_2$, $-NO_2$, $-OR^8$, $-C_1$-C_6alkyl-OH, $-C_1$-C_6alkyl-OR^8, or $-Si(R^{15})_3$;

R^2 is $-C(O)R^9$;

each R^3 is independently halo, -CN, -OH, $-OR^8$, $-NH_2$, $-NHR^8$, $-N(R^8)_2$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^7)_2$, $-S(O)N(R^7)_2$, $-NO_2$, $-Si(R^{12})_3$, $-SF_5$, $-C(O)OR^6$, $-C(O)N(R^7)_2$, $-NR^{12}C(O)R^8$, $-NR^{12}C(O)OR^8$, $-OC(O)N(R^7)_2$, $-OC(O)R^8$, $-C(O)R^6$, $-OC(O)CHR^8N(R^{12})_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl; wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl of R^3 is independently optionally substituted with one to three R^{10};

each R^4 is independently halo, -CN, -OH, $-OR^8$, $-NH_2$, $-NHR^8$, $-N(R^8)_2$, $-S(O)_2R^8$, $-S(O)R^8$, $-S(O)_2N(R^7)_2$, $-S(O)N(R^7)_2$, $-NO_2$, $-Si(R^{15})_3$, $-C(O)OR^6$, $-C(O)N(R^7)_2$, $-NR^{12}C(O)R^8$, $-OC(O)R^8$, $-C(O)R^6$, $-NR^{12}C(O)OR^8$, $-OC(O)N(R^7)_2$, $-OC(O)CHR^8N(R^{12})_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl; wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl of R^4 is optionally independently optionally substituted with one to three R^{10};

R^5 is hydrogen or C_1-C_6alkyl;

each R^6 is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl; wherein each R^6 is independently further substituted with one to three R^{11};

each R^7 is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_6cycloalkyl, -C_2-C_6alkenylC_3-C_6cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, -C_1-C_6alkylheteroaryl, -C_2-C_6alkenylheteroaryl, or two R^7 together with the nitrogen atom to which they are attached, form a 4 to 7 membered heterocyclyl; wherein each R^7 or ring formed thereby is independently further substituted with one to three R^{11};

each R^8 is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, -C_1-C_6alkylC_3-C_{10}cycloalkyl, -C_2-C_6alkenylC_3-C_{10}cycloalkyl, -C_1-C_6alkylheterocyclyl, -C_2-C_6alkenylheterocyclyl, -C_1-C_6alkylaryl, -C_2-C_6alkenylaryl, -C_1-C_6alkylheteroaryl, or -C_2-C_6alkenylheteroaryl; wherein each R^8 is independently further substituted with one to three R^{11};

R^9 is -C_1-C_2haloalkyl, -C_2-C_3alkenyl, -C_2-C_3haloalkenyl, C_2alkynyl, or -$CH_2OS(O)_2$-phenyl, wherein the C_1-C_2alkylhalo and -C_2-C_3alkenylhalo are optionally substituted with one or two -CH_3, and the C_2alkynyl and phenyl are optionally substituted with one -CH_3;

each R^{10} is independently halo, -CN, -OR^{12}, -NO_2, -$N(R^{12})_2$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)N(R^{12})_2$, -$S(O)_2N(R^{12})_2$, -$Si(R^{12})_3$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$OC(O)R^{12}$, -$OC(O)OR^{12}$, -$OC(O)N(R^{12})_2$, -$NR^{12}C(O)OR^{12}$, -$OC(O)CHR^{12}N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{10} is optionally independently substituted with one to three R^{11};

each R^{11} is independently halo, -CN, -OR^{12}, -NO_2, -$N(R^{12})_2$, -$S(O)R^{13}$, -$S(O)_2R^{13}$, -$S(O)N(R^{12})_2$, -$S(O)_2N(R^{12})_2$, -$Si(R^{12})_3$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$OC(O)R^{12}$, -$OC(O)OR^{12}$, -$OC(O)N(R^{12})_2$, -$NR^{12}C(O)OR^{12}$, -$OC(O)CHR^{12}N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl;

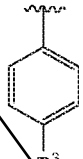
each R^{12} is independently hydrogen, C_1-C_6alkyl or C_3-C_{10}cycloalkyl;

each R^{13} is independently C_1-C_6alkyl or C_3-C_{10}cycloalkyl; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

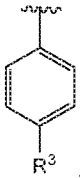
with the proviso that:

(a) when X is NH, R^1 is -$C(O)OR^6$, R^2 is -$C(O)CH_2Cl$ or $C(O)CH_2F$, q is 1, p is 0, and ring A with the R^3



is ; then (i) R^3 and R^6 are not simultaneously $-NO_2$ and $-CH_3$, respectively, and (ii) when R^6 is $-CH_3$, then R^3 is other than H, halo, and $-NO_2$; and

(b) when X is NH, R^1 is $-C(O)OR^6$, R^2 is $-C(O)CH_2Cl$ or $C(O)CH_2F$, q is 1, p is 0, ring A with the R^3 is



, and R^3 is $-C(O)OR^6$; then both R^6 are not simultaneously

(i) $-CH_3$;

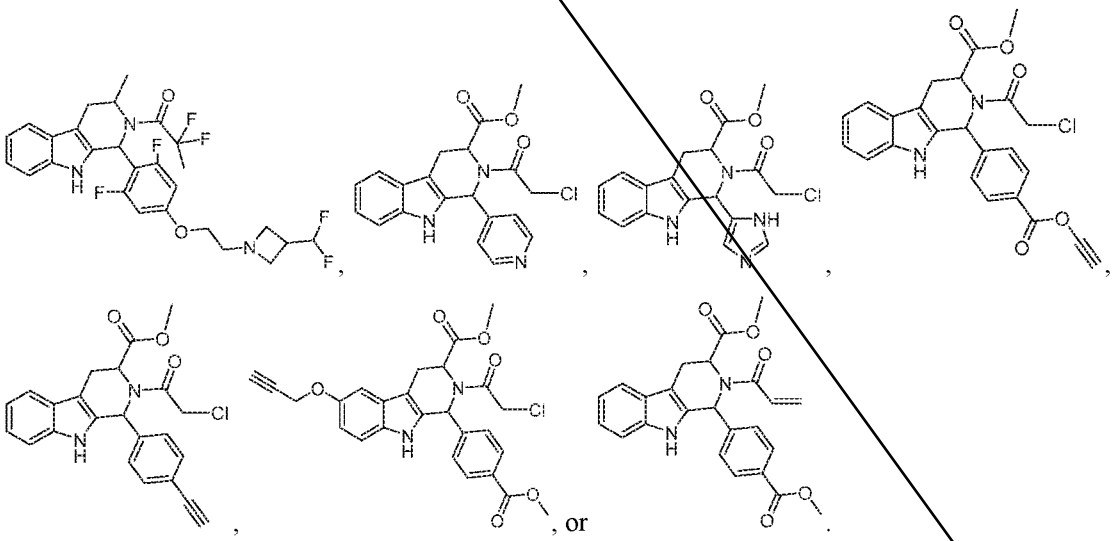
(ii) $-CH_3$ and C_2-C_6alkynyl, respectively; or

(iii) $-CH_2CH_3$ and $-CH_3$, respectively; and

(c) when X is NH, R^1 is $-C(O)OCH_3$, R^2 is $-C(O)CH_2Cl$ or $-C(O)CH_2F$, q is 1, p is 0, and R^3 is H; then ring A is other than phenyl; and

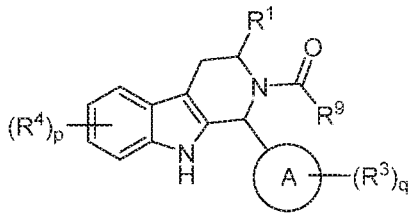
(d) when X is NH, R^1 is $-C(O)N(R^7)_2$, wherein R^7 are H, R^2 is $-C(O)CH_2Cl$ or $-C(O)CH_2F$, q is 1, p is 0, and ring A is phenyl; then R^3 is other than H or halo; and

(e) the compound is not



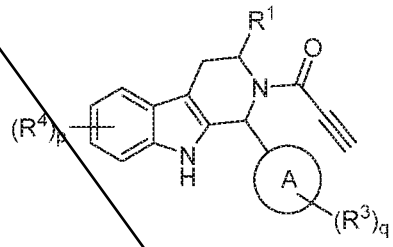
, or .

2. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (II):



(II).

3. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (III):



(III).

4. The compound of any one of claims 1-3, wherein ring A is C_4-C_{10}cycloalkyl.

5. The compound of any one of claims 1-3, wherein ring A is heterocyclyl.

6. The compound of any one of claims 1-3, wherein ring A is aryl.

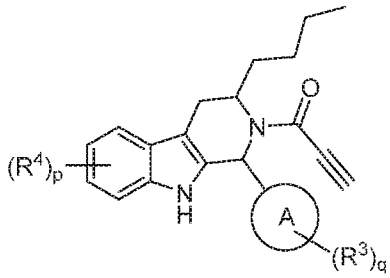
7. The compound of any one of claims 1-3, wherein ring A is heteroaryl.

8. The compound of any one of claims 1-7, wherein R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, -CN, -C(O)OR^6, -C(O)$N(R^7)_2$, -NH_2, -NHR^8, -$N(R^8)_2$, -OH, -OR^8, -C_1-C_6alkyl-OH or -C_1-C_6alkyl-OR^8.

9. The compound of any one of claims 1-8, wherein R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, -NH_2, -NHR^8, -$N(R^8)_2$, -OH, -OR^8, -C_1-C_6alkyl-OH or -C_1-C_6alkyl-OR^8.

10. The compound of any one of claims 1-8, wherein R^1 is -C(O)OR^6 or -C(O)$N(R^7)_2$.

11. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (IV):



(IV).

12. The compound of any one of claims 1-11, wherein each R^4 is independently halo, -CN, -OH, -OR^8, -NH_2, -NHR^8, -$N(R^8)_2$, -$S(O)_2R^8$, -$S(O)R^8$, -$S(O)_2N(R^7)_2$, -$S(O)N(R^7)_2$, -NO_2, -$Si(R^{15})_3$, -C(O)OR^6,

-C(O)N(R^7)$_2$, -NR^{12}C(O)R^8, -OC(O)R^8, -C(O)R^6, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl; wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl of R^4 is independently optionally substituted with one to three R^{10}.

13. The compound of any one of claims 1-12, wherein each R^4 is independently halo, -CN, -OH, -OR^8, C_1-C_6alkyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl; wherein each C_1-C_6alkyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl of R^4 is independently optionally substituted with one to three R^{10}.

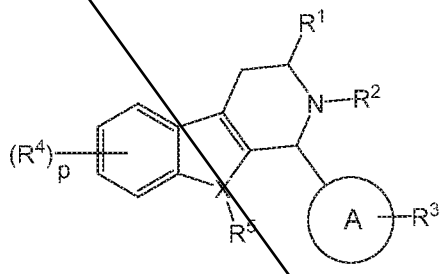
14. The compound of any one of claims 1-11, wherein p is 0.

15. The compound of any one of claims 1-14, wherein q is 0.

16. The compound of any one of claims 1-13 and 15, wherein p is 1, 2 or 3.

17. The compound of any one of claims 1-14 and 16, wherein q is 2 or 3.

18. A compound of formula (V):



(V)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

A is a 4 to 7 membered cycloalkyl, 4 to 7 membered heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^1 is H, C_1-C_6alkyl, -C_1-C_6alkylhalo, –C(O)OR^6, -C(O)N(R^7)$_2$, -OC(O)R^6, -SO_2R^8, -SOR^8, NO_2, -OR^8, -C_1-C_6alkyl-OR^{12}, or -Si(R^{15})$_3$;

R^2 is -C(O)R^9;

R^3 is H, halo, -C(O)OR^{10}, -C(O)N(R^{11})$_2$, -OC(O)R^{10}, -C_0-C_6alkylC_3-C_8cycloalkyl, -C_0-C_6alkylheterocyclyl, -N(R^{11})$_2$, -SO_2R^8, -SOR^8, -NO_2 or -Si(R^{15})$_3$;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –OR^{12}, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^6 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, (R^{11})$_2$NC_1-C_6alkyl-, or (R^{11})$_2$NC_2-C_6alkenyl-;

each R^7 is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-,

heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O$-C_1-C_6alkyl-, or $R^{12}O(O)C$-C_1-C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1-C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^8 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2N$-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two $-CH_3$, or one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl- or $(R^{15})_3SiC_0$-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-;

with the proviso that:

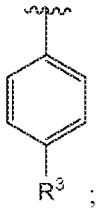
(a) when

X is N;

R^1 is –C(O)OR^6

R^2 is –C(O)CH_2Cl or C(O)CH_2F;

ring A with the R^3 is



;

p is 0; and

R^5 is H;

then (i) R^3 and R^6 are not simultaneously -NO_2 and –CH_3, respectively, and (ii) when R^6 is –CH_3, then R^3 is other than H, halo, and –NO_2; and

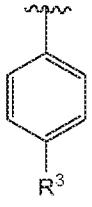
(b) when

X is N;

R^1 is –C(O)OR^6

R^2 is –C(O)CH_2Cl or C(O)CH_2F;

ring A with the R^3 is



;

R^3 is -C(O)OR^{10};

p is 0; and

R^5 is H;

then R^6 and R^{10} are not simultaneously

(i) -CH_3;

(ii) -CH_3 and C_2-C_6alkynyl, respectively; and

(iii) $-CH_2CH_3$ and $-CH_3$, respectively; and

(c) when

X is N;

R^1 is $-C(O)OR^6$, wherein R^6 is $-CH_3$;

R^2 is $-C(O)CH_2Cl$ or $-C(O)CH_2F$;

p is 0;

R^3 is H; and

R^5 is H;

then ring A is other than phenyl; and

(d) when

X is N;

R^1 is $-C(O)N(R^7)_2$, wherein R^7 are H;

R^2 is $-C(O)CH_2Cl$ or $-C(O)CH_2F$;

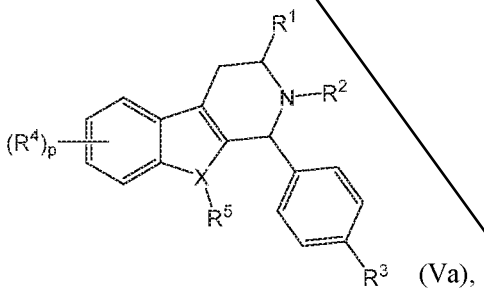
p is 0;

R^5 is H; and

ring A is phenyl;

then R^3 is other than H or halo.

19. The compound of claim 18, having the structure formula (Va):



(Va),

or an enantiomer or pharmaceutically acceptable salt thereof,

wherein:

X is N, O or S;

R^1 is C_1-C_6alkyl, -C_1-C_6alkylhalo, $-C(O)OR^6$, $-C(O)N(R^7)_2$, $-OC(O)R^6$, $-SO_2R^8$, $-SOR^8$, NO_2, $-OR^8$, -C_1-C_6alkyl-OR^{12}, or $-Si(R^{15})_3$;

R^2 is $-C(O)R^9$;

R^3 is $-C(O)OR^{10}$, $-C(O)N(R^{11})_2$, $-OC(O)R^{10}$, -C_0-C_6alkylC_3-C_8cycloalkyl, -C_0-C_6alkylheterocyclyl, $-N(R^{11})_2$, $-SO_2R^8$, $-SOR^8$, $-NO_2$ or $-Si(R^{15})_3$;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12}$, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^6 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2NC_2$-C_6alkenyl-;

each R^7 is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O$-C_1-C_6alkyl-, or $R^{12}O(O)C$-C_1-C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1-C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^8 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2N$-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two $-CH_3$, or one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl- or $(R^{15})_3SiC_0$-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-;

with the proviso that:

(a) when

X is N;

R^1 is –C(O)OR^6

R^2 is –C(O)CH_2Cl or –C(O)CH_2F;

p is 0; and

R^5 is H;

then (i) R^3 and R^6 are not simultaneously-NO_2 and –CH_3, respectively;

(b) when

X is N;

R^1 is –C(O)OR^6

R^2 is –C(O)CH_2Cl or –C(O)CH_2F;

R^3 is -C(O)OR^{10};

p is 0; and

R^5 is H;

then R^6 and R^{10} are not simultaneously

(i) -CH_3;

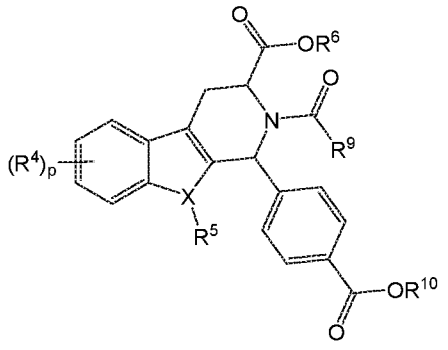
(ii) -CH_3 and C_2-C_6alkynyl, respectively; and

(iii) -CH_2CH_3 and –CH_3, respectively.

20. The compound of claim 18 or 19, wherein R^9 is –C_1-C_2alkylhalo, wherein optionally one or up to all H in -C_1-C_2alkyl is replaced with deuterium.

21. The compound of claim 20, wherein R^9 is –CH_2Cl or –CD_2Cl.

22. The compound of claim 18, having a structure of formula (Vb):



(Vb)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12}$, $-C_1$-C_6alkyl-OR^{12}, $-C_1$-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

R^6 is C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2NC_2$-C_6alkenyl-;

R^9 is $-C_1$-C_2alkylhalo, $-C_2$-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two $-CH_3$, or one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl- or $(R^{15})_3SiC_0$-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-;

with the proviso that when

X is N;

R^9 is –CH_2Cl, –CH_2F, –CD_2Cl, or –CD_2F;

p is 0; and

R^5 is H, then R^6 and R^{10} are not simultaneously

(i) -CH_3;

(ii) -CH_3 and C_2-C_6alkynyl, respectively; and

(iii) -CH_2CH_3 and –CH_3, respectively.

23. The compound of claim 22, wherein R^6 is methyl, ethyl, n-propyl, n-butyl, isopropyl, t-butyl, pentyl, or hexyl.

24. The compound of claim 22, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –OR^{12}, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_1-C_6alkyl;

R^9 is -C_1-C_2alkylCl, wherein optionally one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{10} is C_2-C_6alkyl;

R^{12} is H or C_1-C_6alkyl; and

p is 0, 1, 2 or 3.

25. The compound of claim 22, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –OR^{12}, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-

NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_3-C_6alkyl;

R^9 is $-C_1$-C_2alkylCl, wherein optionally one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl;

R^{12} is H or C_1-C_6alkyl; and

p is 0, 1, 2 or 3.

26. The compound of claim 22, wherein:

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12,}$ $-C_1$-C_6alkyl-OR^{12}, $-C_1$-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_1-C_6alkyl;

R^9 is $-C_1$-C_2alkylCl, wherein optionally one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

R^{10} is C_3-C_6alkyl;

R^{12} is H or C_1-C_6alkyl; and

p is 0, 1, 2 or 3.

27. The compound of claim 22, wherein:

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12,}$ $-C_1$-C_6alkyl-OR^{12}, $-C_1$-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_1-C_6alkyl;

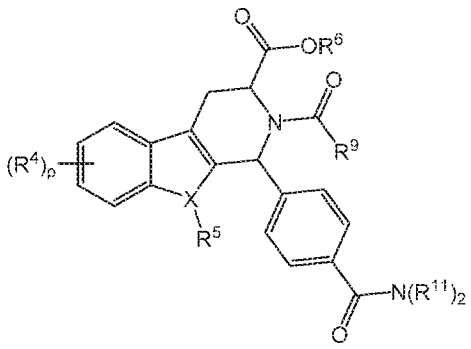
R^9 is $-C_1$-C_2alkylCl, wherein optionally one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium; and

R^{10} is adamantyl or adamantylC_1-C_6aliphatic-;

R^{12} is H or C_1-C_6alkyl; and

p is 0, 1, 2 or 3.

28. The compound of claim 18, having the structure of formula (Vc):



(Vc)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12}$, $-C_1$-C_6alkyl-OR^{12}, $-C_1$-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^6 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2NC_2$-C_6alkenyl-;

R^9 is $-C_1$-C_2alkylhalo, $-C_2$-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two $-CH_3$, or one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-,

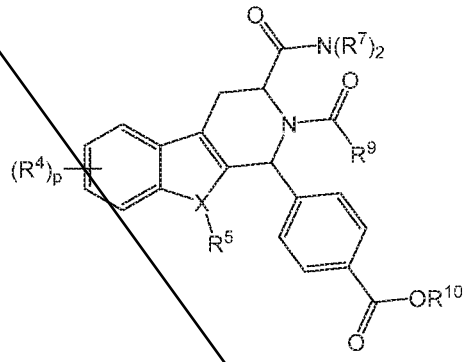
heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-.

29. The compound of claim 18, having a structure of formula (Vd):



(Vd)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^7 is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, R^{12}O-C_1-C_6alkyl-, or R^{12}O(O)C-C_1-C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1-C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2$N-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two –CH_3, or one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-,

heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl- or $(R^{15})_3SiC_0$-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, $-NH_2$, C_1-C_6alkyl, C_1-C_6alkyl-O-, $R^{12}O$-C_1-C_6alkyl(O)C-, and $R^{12}O(O)C$-.

30. The compound of claim 29, wherein:,

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $–OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_1-C_6 alkyl;

R^9 is -C_1-C_2alkylCl, wherein optionally one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{11} are as defined for formula (V) above; and

R^{12} is independently H or C_1-C_6alkyl.

31. The compound of claim 29, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

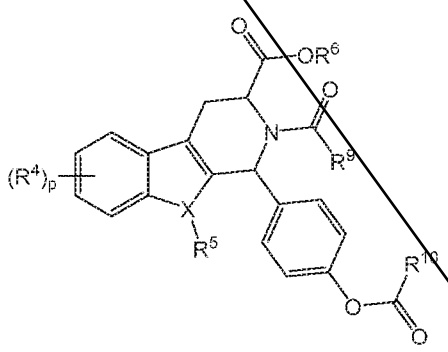
R^7 is as defined for formula (V) above;

R^9 is -C_1-C_2alkylCl, wherein optionally one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

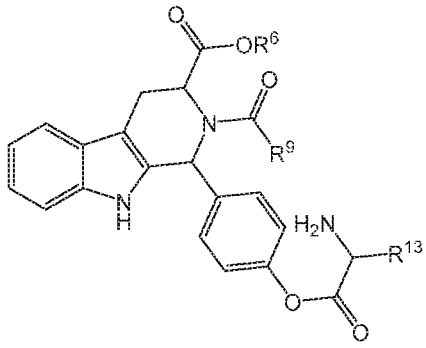
R^{10} is C_1-C_6alkyl; and

R^{12} is independently H or C_1-C_6alkyl.

32. The compound of claim 18, having a structure of formula (Ve) or (Vf):



(Ve)



(Vf)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

R^6 is C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2NC_2$-C_6alkenyl-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two –CH_3, or one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl- or $(R^{15})_3SiC_0$-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2N$$C_1$-$C_6$alkyl-, $(R^{11})_2N$$C_2$-$C_6$alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, -NH_2, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, $R^{12}O$-C_1-C_6alkyl(O)C-, and $R^{12}O(O)C$-.

33. The compound of claim 32, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -$OC(O)R^{12}$;

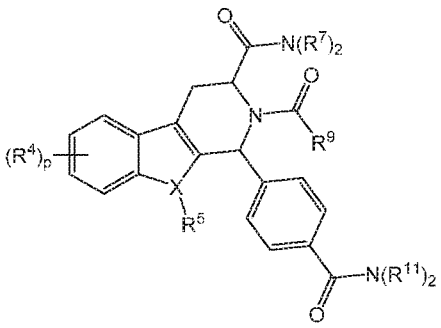
R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

R^6 is C_1-C_6alkyl;

R^9 is -C_1-C_2alkylCl, wherein optionally one or up to all H in -C_1-C_2alkyl is replaced with deuterium; and

R^{10}, R^{12} and R^{13} are as defined for the compound of formula (Ve) or (Vf).

34. The compound of claim 18, having a structure of formula (Vg):



(Vg)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12}$, $-C_1$-C_6alkyl-OR^{12}, $-C_1$-C_6alkyl-NR^{12} or $-OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^7 is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O$-C_1-C_6alkyl-, or $R^{12}O(O)C$-C_1-C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1-C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

R^9 is $-C_1$-C_2alkylhalo, $-C_2$-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two $-CH_3$, or one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

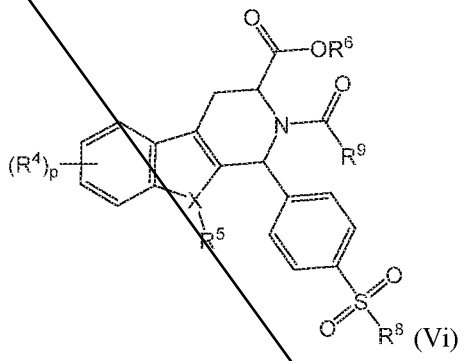
each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-.

35. The compound of claim 18, having as structure of formula (Vi):



(Vi)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

R^6 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2NC_2$-C_6alkenyl-;

R^8 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2N$-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally

substituted with one or two halo, one or two $-CH_3$, or one or up to all H in $-C_1$-C_2alkyl is replaced with deuterium;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2N$$C_1$-$C_6$alkyl-, $(R^{11})_2N$$C_2$-$C_6$alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

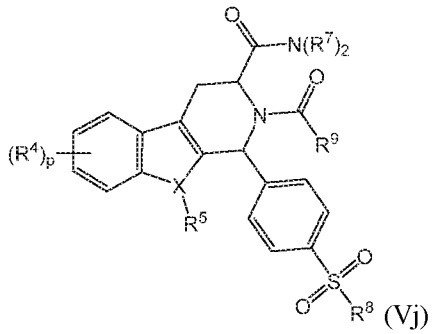
each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, $-NH_2$, C_1-C_6alkyl, C_1-C_6alkyl-O-, $R^{12}O$-C_1-C_6alkyl(O)C-, and $R^{12}O(O)C$-.

36. The compound of claim 18, having a structure of formula (Vj):



(Vj)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –$OR^{12,}$ -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

each R^7 is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O$-C_1-C_6alkyl-, or $R^{12}O(O)C$-C_1-C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1-C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

R^8 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $(R^{11})_2NC_1$-C_6alkyl-, or $(R^{11})_2N$-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two –CH_3, or one or up to all H in -C_1-C_2alkyl is replaced with deuterium;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, -NH_2, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

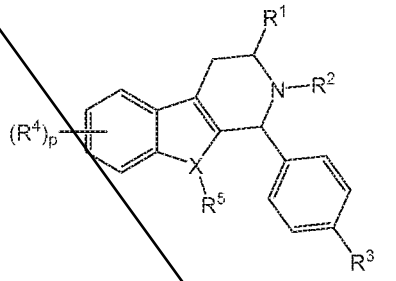
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen,

oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-.

37. The compound of claim 18, having a structure of formula (Vn):



(Vn),

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^1 is C_1-C_6alkyl, -C_1-C_6alkylhalo, or -C_1-C_6alkyl-OR^{12};

R^2 is -C(O)R^9;

R^3 is -C(O)OR^{10}, -C(O)N(R^{11})$_2$, -OC(O)R^{10}, -C_0-C_6alkylC_3-C_8cycloalkyl, -C_0-C_6alkylheterocyclyl, -N(R^{11})$_2$, -SO_2R^8, -SOR^8, -NO_2 or -Si(R^{15})$_3$;

R^4 is independently halo, CN, -NH_2, -SO_2, C_1-C_8alkyl, –OR^{12}, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -OC(O)R^{12};

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

R^8 is independently C_1-C_6alkyl, C_3-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, (R^{11})$_2$NC_1-C_6alkyl-, (R^{11})$_2$N-, or $R^{14}C_0$-C_6alkyl-;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two –CH_3, or one or up to all H is replaced with deuterium;

R^{10} is C_1-C_6alkyl, C_2-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, (R^{11})$_2$NC_1-C_6alkyl-, (R^{11})$_2$NC_2-C_6alkenyl-, R^{13}(NH_2)CH-, $R^{14}C_0$-C_6alkyl-, or (R^{15})$_3$SiC_0-C_6alkyl-;

each R^{11} is independently H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, heterocyclyl, aryl,

heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, $R^{12}O$-C_1-C_6alkyl-, $(R^{11})_2NC_1$-C_6alkyl-, $(R^{11})_2NC_2$-C_6alkenyl-, $R^{12}O(O)C$-C_1-C_6alkyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$-C_6alkyl-, $(R^{15})_3SiC_0$-C_6alkyl-, or an N-protecting group; or two R^{11} together with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1 or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1-C_6alkyl, C_1-C_6alkyl-O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $-NH_2$, or C_1-C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1-C_6alkyl;

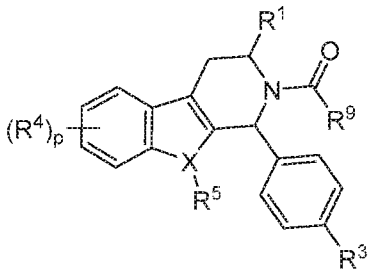
each R^{13} is independently H, C_1-C_6alkyl, C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3-C_6cycloalkylC_1-C_6alkyl-, C_3-C_6cycloalkylC_2-C_6alkenyl-, heterocyclylC_1-C_6alkyl-, heterocyclylC_2-C_6alkenyl-, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, heteroarylC_2-C_6alkenyl-, adamantyl, adamantylC_1-C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-;

wherein the C_1-C_6alkyl, -C_3-C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, $-NH_2$, C_1-C_6alkyl, C_1-C_6alkyl-O-, $R^{12}O$-C_1-C_6alkyl(O)C-, and $R^{12}O(O)C$-.

38. The compound of claim 18, having a structure of formula (Vp):



(Vp)

or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O or S;

R^1 is C_1-C_6alkyl, -C_1-C_6alkylhalo, or -C_1-C_6alkyl-OR^{12};

R^3 is -C_0-C_6alkylC_3-C_8cycloalkyl or -C_0-C_6alkylheterocyclyl;

R^4 is independently halo, CN, $-NH_2$, $-SO_2$, C_1-C_8alkyl, $-OR^{12}$, -C_1-C_6alkyl-OR^{12}, -C_1-C_6alkyl-NR^{12} or -$OC(O)R^{12}$;

R^5 is H, C_1-C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2 or 3;

R^9 is -C_1-C_2alkylhalo, -C_2-C_3alkenylhalo, or C_2alkynyl, wherein the C_1-C_2alkyl is optionally substituted with one or two halo, one or two –CH_3, or one or up to all H is replaced with deuterium;

R^{12} is independently H or C_1-C_6alkyl;

wherein the C_0-C_6alkyl or -C_3-C_8cycloalkyl are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, -NH_2, C_1-C_6alkyl, C_1-C_6alkyl-O-, R^{12}O-C_1-C_6alkyl(O)C-, and R^{12}O(O)C-.

39. A compound selected from the group consisting of compounds listed in Table 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition comprising a compound, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 39, and a pharmaceutically acceptable carrier.

41. A method of inhibiting GPX4 in a cell, comprising contacting a cell with an effective amount of a compound, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 39.

42. The method of claim 41, wherein the cell is a cancer cell.

43. A method of treating cancer in a subject, comprising administering to a subject having cancer a therapeutically effective amount of a compound, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, of any one of claims 1 to 39.

44. The method of claim 43, wherein the cancer is adrenocortical cancer, anal cancer, biliary cancer, bladder cancer, bone cancer, brain cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, head and neck cancer, intestinal cancer, liver cancer, lung cancer, oral cancer, ovarian cancer, pancreatic cancer, renal cancer, prostate cancer, salivary gland cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, sarcoma, or a soft tissue carcinoma.

45. The method of claim 44, wherein the cancer is osteosarcoma, glioma, astrocytoma, neuroblastoma, cancer of the small intestine, bronchial cancer, small cell lung cancer, non-small cell lung cancer, basal cell carcinoma, or melanoma.

46. The method of claim 45, wherein the cancer is a the hematologic cancer.

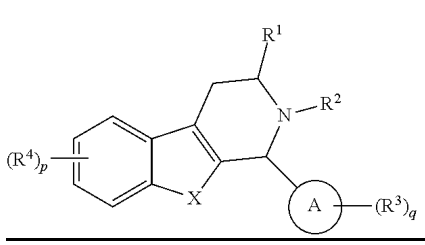
47. The method of claim 45, wherein the hematologic cancer is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphoma (e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Burkitt's lymphoma), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), Hairy Cell chronic myelogenous leukemia (CML), or multiple myeloma.

48. The method of any one of claims 43 to 47, further comprising administering a therapeutically effective amount of a second therapeutic agent.

49. The method of claim 48, wherein the second therapeutic agent is an platinating agent, alkylating agent, anti-cancer antibiotic, antimetabolite, topoisomerase I inhibitor, topoisomerase II inhibitor, or antimicrotubule agent.

What is claimed is:

1. A compound of formula (I):



(I)

or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, wherein:

ring A is C_4-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is NR^5, O, or S;

p is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, —CN, —OH, —C(O)OR^6, —C(O)$N(R^7)_2$, —$OC(O)R^6$, —$S(O)_2R^8$, —$S(O)_2N(R^7)_2$, —S(O)$N(R^7)_2$, —S(O)R^8, —NH_2, —NHR^8, —$N(R^8)_2$, —NO_2, —OR^8, —C_1-C_6alkyl-OH, —C_1-C_6alkyl-OR^8, or —$Si(R^{15})_3$;

R^2 is —C(O)R^9;

each R^3 is independently halo, —CN, —OH, —OR^8, —NH_2, —NHR^8, —N(R)$_2$, —$S(O)_2R^8$, —S(O)R^8, —$S(O)_2N(R^7)_2$, —S(O)$N(R^7)_2$, —NO_2, —$Si(R^{12})_3$, —SF_5, —C(O)OR^6, —C(O)$N(R^7)_2$, —$NR^{12}C(O)R^8$, —$NR^{12}C(O)OR^8$, —$OC(O)N(R^7)_2$, —$OC(O)R^8$, —C(O)R^6, —$OC(O)CHR^8N(R^{12})_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl, wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl of R^3 is independently optionally substituted with one to three R^{10};

each R^4 is independently halo, —CN, —OH, —OR^8, —NH_2, —NHR^8, —N(R)$_2$, —$S(O)_2R^8$, —S(O)R^8, —$S(O)_2N(R^7)_2$, —S(O)$N(R^7)_2$, —NO_2, —$Si(R^{15})_3$, —C(O)OR^6, —C(O)$N(R^7)_2$, —$NR^{12}C(O)R^8$, —$OC(O)R^8$, —C(O)R^6, —$NR^{12}C(O)OR^8$, —$OC(O)N(R^7)_2$, —$OC(O)CHR^8N(R^{12})_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, C_1-

C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl, wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl of R^4 is independently optionally substituted with one to three R^{10};

R^5 is hydrogen or C_1-C_6alkyl;

each R^6 is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl; wherein each R^6 is optionally independently further substituted with one to three R^{11};

each R^7 is independently hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_6cycloalkyl, —C_2-C_6alkenylC_3-C_6cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, —C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl, or two R^7 together with the nitrogen atom to which they are attached form a 4- to 7- membered heterocyclyl, wherein each R^7 or ring formed thereby is optionally independently further substituted with one to three R^{11};

each R^8 is independently C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, heteroaryl, —C_1-C_6alkylC_3-C_{10}cycloalkyl, —C_2-C_6alkenylC_3-C_{10}cycloalkyl, —C_1-C_6alkylheterocyclyl, —C_2-C_6alkenylheterocyclyl, —C_1-C_6alkylaryl, —C_2-C_6alkenylaryl, —C_1-C_6alkylheteroaryl, or —C_2-C_6alkenylheteroaryl, wherein each R^8 is optionally independently further substituted with one to three R^{11};

R^9 is C_2alkynyl optionally substituted with one —CH_3;

each R^{10} is independently halo, —CN, —OR^{12}, —NO_2, —$N(R^{12})_2$, —$S(O)R^{13}$, —$S(O)_2R^{13}$, —$S(O)N(R^{12})_2$, —$S(O)_2N(R^{12})_2$, —$Si(R^{12})_3$, —$C(O)R^{12}$, —$C(O)OR^{12}$, —$C(O)N(R^{12})_2$, —$NR^{12}C(O)R^{12}$, —$OC(O)R^{12}$, —$OC(O)OR^{12}$, —$OC(O)N(R^{12})_2$, —$NR^{12}C(O)OR^{12}$, —$OC(O)CHR^{12}N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl of R^{10} is optionally independently substituted with one to three R^{11};

each R^{11} is independently halo, —CN, —OR^{12}, —NO_2, —$N(R^{12})_2$, —$S(O)R^{13}$, —$S(O)_2R^{13}$, —$S(O)N(R^{12})_2$, —$S(O)_2N(R^{12})_2$, —$Si(R^{12})_3$, —$C(O)R^{12}$, —$C(O)OR^{12}$, —$C(O)N(R^{12})_2$, —$NR^{12}C(O)R^{12}$, —$OC(O)R^{12}$, —$OC(O)OR^{12}$, —$OC(O)N(R^{12})_2$, —$NR^{12}C(O)OR^{12}$, —$OC(O)CHR^{12}N(R^{12})_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_{10}cycloalkyl, heterocyclyl, aryl, or heteroaryl;

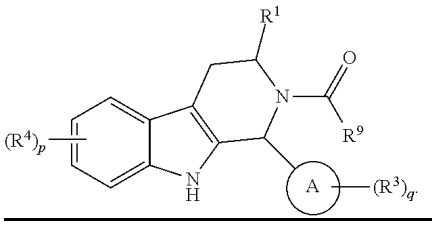
each R^{12} is independently hydrogen, C_1-C_6alkyl or C_3-C_{10}cycloalkyl;

each R^{13} is independently C_1-C_6alkyl, or C_3-C_{10}cycloalkyl; and

each R^{15} is independently C_1-C_6alkyl, C_2-C_6alkenyl, aryl, heteroaryl, arylC_1-C_6alkyl-, arylC_2-C_6alkenyl-, heteroarylC_1-C_6alkyl-, and heteroarylC_2-C_6alkenyl-.

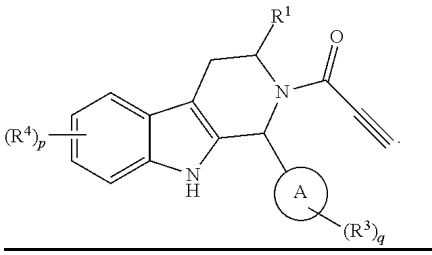
2. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (II):

(II)



3. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (III):

(III)



4. The compound of claim 1, wherein ring A is C_4-C_{10}cycloalkyl.

5. The compound of claim 1, wherein ring A is heterocyclyl.

6. The compound of claim 1, wherein ring A is aryl.

7. The compound of claim 1, wherein ring A is heteroaryl.

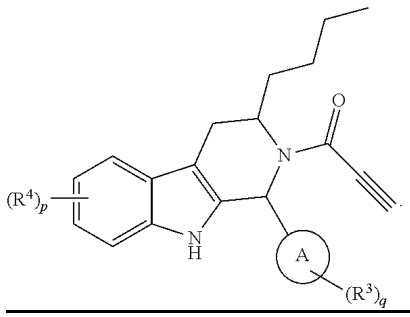
8. The compound of claim 1, wherein R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, —CN, —C(O)OR^6, —C(O)N$(R^7)_2$, —NH_2, —NHR^8, —N$(R^8)_2$, —OH, —OR^8, —C_1-C_6alkyl-OH, or —C_1-C_6alkyl-OR^8.

9. The compound of claim 1, wherein R^1 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, C_3-C_{10}cycloalkyl, —NH_2, —NHR^8, —$N(R^8)_2$, —OH, —OR^8, —C_1-C_6alkyl-OH, or —C_1-C_6alkyl-OR^8.

10. The compound of claim 1, wherein R^1 is C_1-C_6alkyl.

11. The compound of claim 1, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, represented by formula (IV):

(IV)



12. The compound of claim 1, wherein each R^4 is independently halo, —CN, —OH, —OR^8, —NH_2, —NHR^8, —$N(R)_2$, —$S(O)_2R^8$, —$S(O)R^8$, —$S(O)_2N(R^7)_2$, —$S(O)N(R^7)_2$, —NO_2, —$Si(R^{15})_3$, —$C(O)OR^6$, —$C(O)N(R^7)_2$, —$NR^{12}C(O)R^8$, —$OC(O)R^8$, —$C(O)R^6$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl, wherein each C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl of R^4 is independently optionally substituted with one to three R^{10}.

13. The compound of claim 1, wherein each R^4 is independently halo, —CN, —OH, —OR^8, C_1-C_6alkyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl, wherein each C_1-C_6alkyl, C_2-C_6alkynyl, or C_3-C_{10}cycloalkyl of R^4 is independently optionally substituted with one to three R^{10}.

14. The compound of claim 1, wherein p is 0.

15. The compound of claim 1, wherein q is 0.

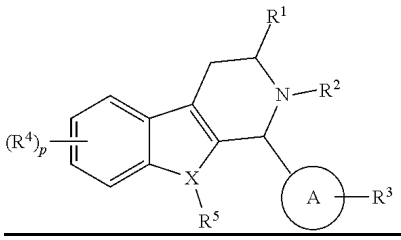
16. The compound of claim 1, wherein p is 1, 2, or 3.

17. The compound of claim 1, wherein q is 2 or 3.

18. A pharmaceutical composition comprising a compound, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, of claim 1, and a pharmaceutically acceptable carrier.

19. A compound of formula (V):

(V)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

A is a 4- to 7-membered cycloalkyl, 4- to 7-membered heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^1 is H, C_1—C_6alkyl, —C_1—C_6alkylhalo, —C(O)OR^6, —C(O)$N(R^7)_2$, —OC(O)R^6, —SO_2R^8, —SOR^8, NO_2, —OR^8, —C_1—C_6alkyl—OR^{12}, or —$Si(R^{15})_3$;

R^2 is —C(O)R^9;

R^3 is H, halo, —C(O)OR^{10}, —C(O)$N(R^{11})_2$, —OC(O)R^{10}, —C_0—C_6alkylC_3—C_8cycloalkyl, —C_0-C_6alkylheterocyclyl, —$N(R^{11})_2$, —SO_2R^8, —SOR^8, —NO_2, or —$Si(R^{15})_3$;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12},—C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl—NR^{12}, or —OC(O)R^{12};

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2, or 3;

each R^6 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkynyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl—, or $(R^{11})_2NC_2$—C_6alkenyl-;

each R^7 is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O$—C_1—C_6alkyl-, or $R^{12}O(O)C$—C_1—C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1—C_6alkyl,

a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$-, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^8 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2N$-;

R^9 is C_2alkynyl;

R^{10} is C_1—C_6alkyl, C_2—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$—C_6alkyl-, or $(R^{15})_3SiC_0$—C_6alkyl-;

each R^{11} is independently H, C_1—C_6alkyl, C_2C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $R^{12}O$—C_1—C_6alkyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O(O)C$—C_1—C_6alkyl—, $R^{13}(NH_2)CH$—, $R^{14}C_0$—C_6alkyl—, $(R^{15})_3SiC_0$—C_6alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1C_6alkyl, C_1—C_6alkyl-O(O)C—, $(R^{11})_2N$—, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, —NH_2, or C_1—C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N- protecting group;

each R^{12} is independently H or C_1—C_6alkyl;

each R^{13} is independently H, C_1—C_6alkyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, or an N protecting group;

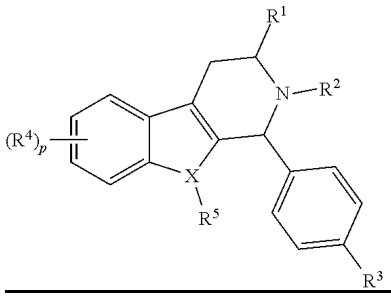
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1—C_6alkyl, C_2—C_6alkenyl, aryl, heteroaryl, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, or heteroarylC_2—C_6alkenyl-;

wherein each C_1—C_6alkyl, —C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl—O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

20. The compound of claim 19, having the structure formula (Va):

(Va)



or an enantiomer or pharmaceutically acceptable salt thereof,

wherein:

X is N, O, or S;

R^1 is C_1—C_6alkyl, —C_1—C_6alkylhalo, —$C(O)OR^6$, —$C(O)N(R^7)_2$, —$OC(O)R^6$, —SO_2R^8, —SOR^8, NO_2, —OR^8, —C_1—C_6alkyl—OR^{12}, or —$Si(R^{15})_3$;

R^2 is —$C(O)R^9$;

R^3 is —$C(O)OR^{10}$, —$C(O)N(R^{11})_2$, —$OC(O)R^{10}$, —C_0—C_6alkylC_3—C_8cycloalkyl, —C_0—C_6alkylheterocyclyl, —$N(R^{11})_2$, —SO_2R^8, —SOR^8, —NO_2, or —$Si(R^{15})_3$;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12}, —C_1—C_6alkyl—OR^{12}, —C_1—C_6alkyl—NR^{12}, or —$OC(O)R^{12}$;

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2, or 3;

each R^6 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2-C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2NC_2$—C_6alkenyl-;

each R^7 is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O$—C_1—C_6alkyl-, or $R^{12}O(O)C$—C_1—C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1—C_6alkyl,

a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$—, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^8 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2N$-;

R^9 is C_2alkynyl;

R^{10} is C_1—C_6alkyl, C_2—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{13}(NH_2)CH$-, $R^{14}C_0$–C_6alkyl-, or $(R^{15})_3Si\ C_0$—C_6alkyl-;

each R^{11} is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $R^{12}O$—C_1—C_6alkyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O(O)C$—C_1—C_6alkyl- , $R^{13}(NH_2)CH$—, $R^{14}C_0$—C_6alkyl-, $(R^{15})_3SiC_0$—C_6alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1—C_6alkyl, C_1—C_6alkyl—O(O)C-, $(R^{11})_2N$-, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, —NH_2, or C_1—C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1—C_6alkyl;

each R^{13} is independently H, C_1—C_6alkyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, or an N protecting group;

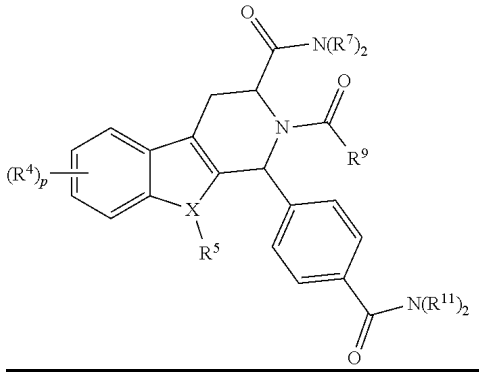
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1—C_6alkyl, C_2—C_6alkenyl, aryl heteroaryl, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, or heteroarylC_2—C_6alkenyl-;

wherein each C_1—C_6alkyl, —C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl—O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

21. The compound of claim 19, having a structure of formula (Vg):

(Vg)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12}, —C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl-NR^{12}, or —$OC(O)R^{12}$;

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2, or 3;

each R^7 is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O$—C_1—C_6alkyl-, or $R^{12}O(O)C$—C_1—C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1—C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$—, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

R^9 is C_2alkynyl;

each R^{11} is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $R^{12}O$—C_1—C_6alkyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O(O)C$—C_1—C_6alkyl- , $R^{13}(NH_2)CH$—, $R^{14}C_0$—C_6alkyl-, $(R^{15})_3SiC_0$—C_6alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered

heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1—C_6alkyl, C_1—C_6alkyl—O(O)C—, $(R^{11})_2N$—, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, —NH_2, or C_1—C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1—C_6alkyl;

each R^{13} is independently H, C_1—C_6alkyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, or an N protecting group;

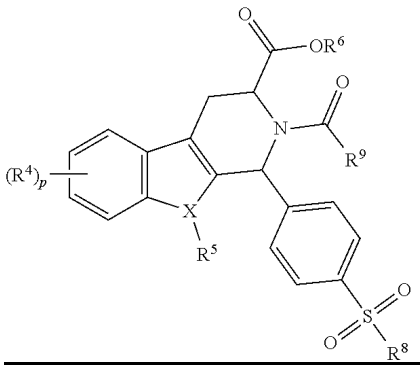
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

R^{15} is independently C_1—C_6alkyl, C_2—C_6alkenyl, aryl, heteroaryl, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, or heteroarylC_2—C_6alkenyl-;

wherein each C_1—C_6alkyl, —C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl—O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

22. The compound of claim 19, having as structure of formula (Vi):

(Vi)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —$OR^{12,}$ —C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl-NR^{12}, or —$OC(O)R^{12}$;

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2, or 3;

R^6 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2NC_2$—C_6alkenyl-;

R^8 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2N$—;

R^9 is C_2alkynyl;

each R^{11} is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $R^{12}O$—C_1—C_6alkyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O(O)C$—C_1—C_6alkyl- , $R^{13}(NH_2)CH$—, $R^{14}C_0$—C_6alkyl-, $(R^{15})_3SiC_0$—C_6alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1—C_6alkyl, C_1—C_6alkyl-O(O)C—, $(R^{11})_2N$—, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, —NH_2, or C_1—C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1—C_6alkyl;

each R^{13} is independently H, C_1—C_6alkyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, or an N protecting group;

R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

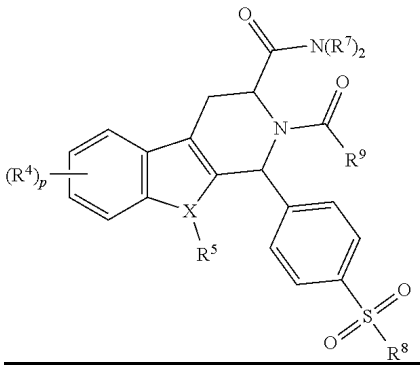
R^{15} is independently C_1—C_6alkyl, C_2—C_6alkenyl, aryl, heteroaryl, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, or heteroarylC_2—C_6alkenyl-;

wherein each C_1—C_6alkyl, —C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted

with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl—O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

23. The compound of claim 19, having a structure of formula (Vj):

(Vj)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12}, —C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl-NR^{12}, or —$OC(O)R^{12}$;

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

P is 0, 1, 2, or 3;

each R^7 is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, $(R^{11})_2NC_1$—C_6alkyl-, $(R^{11})_2NC_2$—C_6alkenyl-, $R^{12}O$—C_1—C_6alkyl-, or $R^{12}O(O)C$—C_1—C_6alkyl-, or two R^7 together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^7 groups is optionally substituted with OH, halo, C_1—C_6alkyl, a 4- to 6-membered heterocyclyl, or $(R^{11})_2N$—, wherein the 4- to 6-membered heterocyclyl when containing 2 or more N atoms is optionally substituted with an N-protecting group;

R^8 is independently C_1—C_6alkyl, C_3—C_6, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, $(R^{11})_2NC_1$—C_6alkyl-, or $(R^{11})_2N$-;

R^9 is C_2alkynyl;

each R^{11} is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-,

$R^{12}O—C_1—C_6$alkyl-, $(R^{11})_2NC_1—C_6$alkyl-, $(R^{11})_2NC_2—C_6$alkenyl-, $R^{12}O(O)C—C_1—C_6$alkyl- , $R^{13}(NH_2)CH—$, $R^{14}C_0—C_6$alkyl-, $(R^{15})_3SiC_0—C_6$alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, $C_1—C_6$alkyl, $C_1—C_6$alkyl-O(O)C—, $(R^{11})_2N—$, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, $—NH_2$, or $C_1—C_6$alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or $C_1—C_6$alkyl;

each R^{13} is independently H, $C_1—C_6$alkyl, $C_3—C_6$cycloalkyl, heterocyclyl, aryl, heteroaryl, $C_3—C_6$cycloalkyl$C_1—C_6$alkyl-, $C_3—C_6$cycloalkyl$C_2—C_6$alkenyl-, heterocyclyl$C_1—C_6$alkyl-, heterocyclyl$C_2—C_6$alkenyl-, aryl$C_1—C_6$alkyl-, aryl$C_2—C_6$alkenyl-, heteroaryl$C_1—C_6$alkyl-, heteroaryl$C_2—C_6$alkenyl—, adamantyl, adamantyl$C_1—C_6$aliphatic-, or an N protecting group;

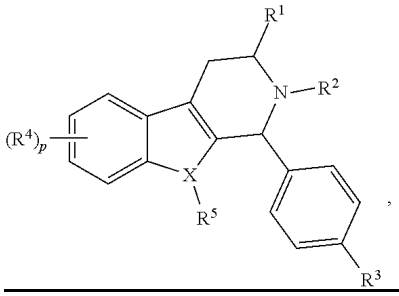
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently $C_1—C_6$alkyl, $C_2—C_6$alkenyl, aryl, heteroaryl, aryl$C_1—C_6$alkyl-, aryl$C_2—C_6$alkenyl-, heteroaryl$C_1—C_6$alkyl-, or heteroaryl$C_2—C_6$alkenyl-;

wherein each $C_1—C_6$alkyl, $—C_3—C_6$cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, $—NH_2$, $C_1—C_6$alkyl, $C_1—C_6$alkyl-O—, $R^{12}O—C_1—C_6$alkyl(O)C—, and $R^{12}O(O)C—$.

24. The compound of claim 19, having a structure of formula (Vn):

(Vn)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

R^1 is $C_1—C_6$alkyl, $—C_1—C_6$alkylhalo, or $—C_1—C_6$alkyl-OR^{12};

R^2 is $—C(O)R^9$;

R^3 is —C(O)OR^{10}, —C(O)N(R^{11})$_2$, —OC(O)R^{10}, —C_0—C_6alkylC_3—C_8cycloalkyl, —C_0—C_6alkylheterocyclyl, —N(R^{11})$_2$, —SO_2R^8, —SOR^8, —NO_2, or —Si(R^{15})$_3$;

R^4 is independently halo, CN, —NH_2, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12}, —C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl-NR^{12}, or —OC(O)R^{12};

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

p is 0, 1, 2, or 3;

R^8 is independently C_1—C_6alkyl, C_3—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, (R^{11})$_2$NC_1—C_6alkyl-, (R^{11})$_2$N—, or $R^{14}C_0$—C_6alkyl-;

R^9 is C_2alkynyl;

R^{10} is C_1—C_6alkyl, C_2—C_6alkyl, C_2—C_6alkenyl, C_2—C_6alkynyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, (R^{11})$_2$NC_1—C_6alkyl-, (R^{11})$_2$NC_2—C_6alkenyl-, R^{13}(NH_2)CH—, $R^{14}C_0$—C_6alkyl-, or (R^{15})$_3$SiC_0—C_6alkyl-;

each R^{11} is independently H, C_1—C_6alkyl, C_2—C_6alkenyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, C_3—C_6cycloalkylC_1—C_6alkyl-, C_3—C_6cycloalkylC_3—C_6cycloalkylC_2—C_6alkenyl-, heterocyclylC_1—C_6alkyl-, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, R^{12}O—C_1—C_6alkyl-, (R^{11})$_2$NC_1—C_6alkyl-, (R^{11})$_2$NC_2—C_6alkenyl-, R^{12}O(O)C—C_1—C_6alkyl- , R^{13}(NH_2)CH—, $R^{14}C_0$—C_6alkyl-, (R^{15})$_3$SiC_0—C_6alkyl-, or an N-protecting group, or two R^{11} together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclyl, wherein the heterocyclyl formed by the two R^{11} groups has optionally 0, 1, or 2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, and the heterocyclyl is optionally substituted with OH, halo, C_1—C_6alkyl, C_1—C_6alkyl-O(O)C—, (R^{11})$_2$N—, or a 4- to 6-membered heterocyclyl, wherein the 4- to 6-membered heterocyclyl is optionally substituted with OH, halo, —NH_2, or C_1—C_6alkyl, or when containing 2 or more N atoms is optionally substituted with an N-protecting group;

each R^{12} is independently H or C_1—C_6alkyl;

each R^{13} is independently H, C_3—C_6alkyl, C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, heterocyclylC_2—C_6alkenyl-, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, heteroarylC_2—C_6alkenyl-, adamantyl, adamantylC_1—C_6aliphatic-, or an N protecting group;

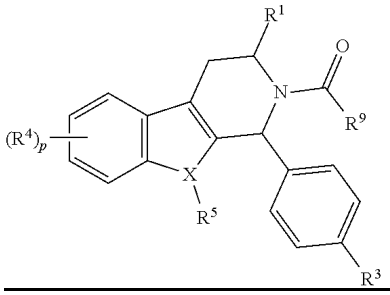
R^{14} is a bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^{15} is independently C_1—C_6alkyl, C_2—C_6alkenyl, aryl, heteroaryl, arylC_1—C_6alkyl-, arylC_2—C_6alkenyl-, heteroarylC_1—C_6alkyl-, or heteroarylC_2—C_6alkenyl-;

wherein each C_1—C_6alkyl, —C_3—C_6cycloalkyl, heterocyclyl, aryl, heteroaryl, or bridged bicyclic ring, by itself or attached to another moiety, are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl-O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

25. The compound of claim 19, having a structure of formula (Vp):

(Vp)



or an enantiomer or pharmaceutically acceptable salt thereof, wherein:

X is N, O, or S;

R^1 is C_1—C_6alkyl, —C_1—C_6alkylhalo, or —C_1—C_6alkyl-OR^{12};

R^3 is —C_0—C_6alkylC_3—C_8cycloalkyl, or —C_0—C_6alkylheterocyclyl;

R^4 is independently halo, CN, —NH_2, —SO_2, C_1—C_8alkyl, —OR^{12}, —C_1—C_6alkyl-OR^{12}, —C_1—C_6alkyl-NR^{12}, or —$OC(O)R^{12}$;

R^5 is H, C_1—C_6alkyl, or is absent when X is S or O;

0, 1, 2, or 3;

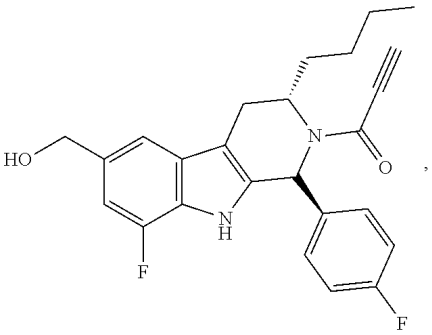
R^9 is C_2alkynyl;

R^{12} independently H or C_1—C_6alkyl;

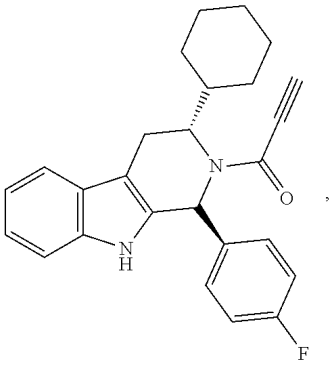
wherein each C_0—C_6alkyl or —C_3—C_8cycloalkyl are independently optionally substituted with 1-3 substituents selected from the group consisting of OH, halo, —NH_2, C_1—C_6alkyl, C_1—C_6alkyl-O—, $R^{12}O$—C_1—C_6alkyl(O)C—, and $R^{12}O(O)C$—.

26. A compound, or a tautomer, stereoisomer, mixture of stereoisomers, isotopically enriched analog, or pharmaceutically acceptable salt thereof, selected from:

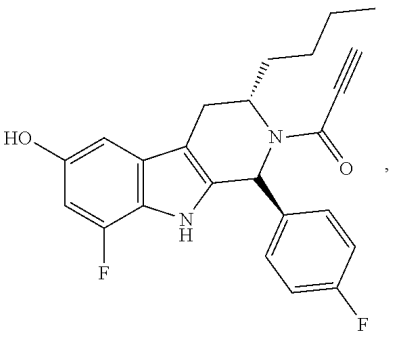
Compound 134



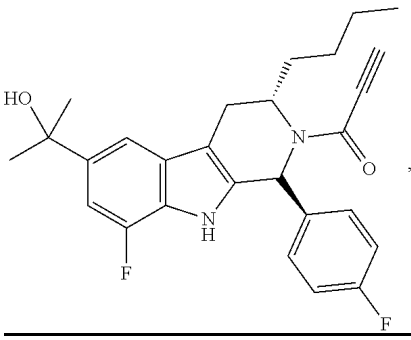
Compound 135



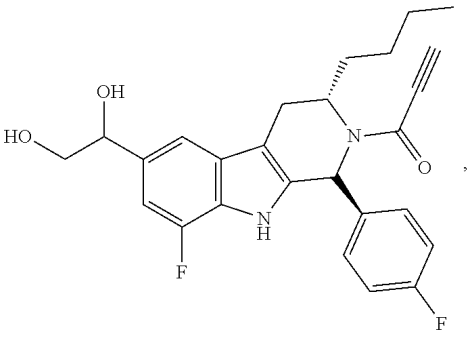
Compound 136



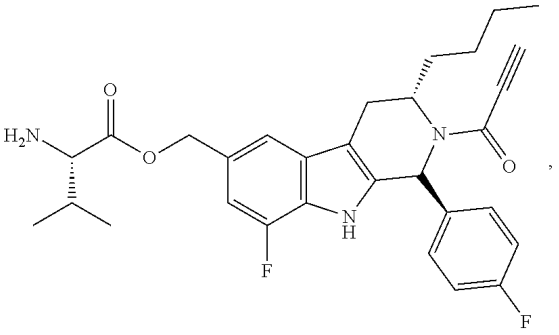
Compound 137



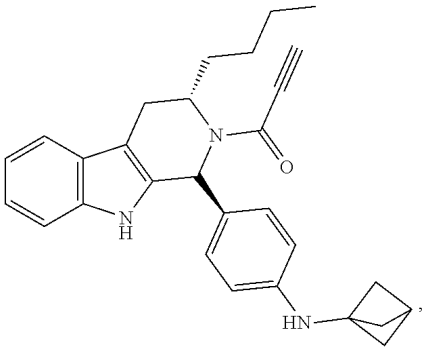
Compound 138



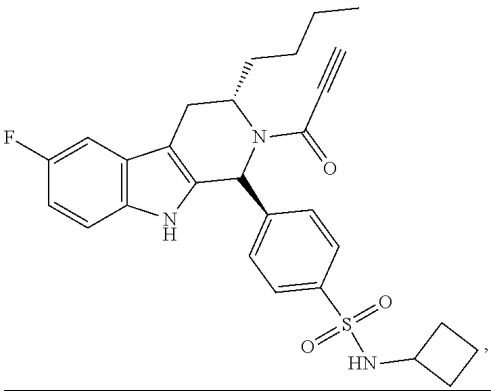
Compound 139



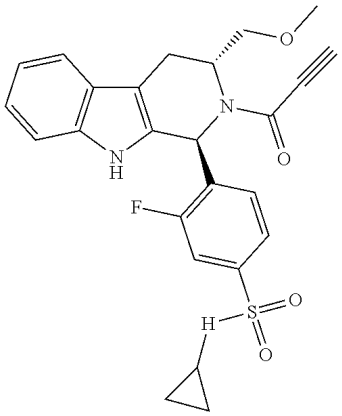
Compound 140



Compound 143

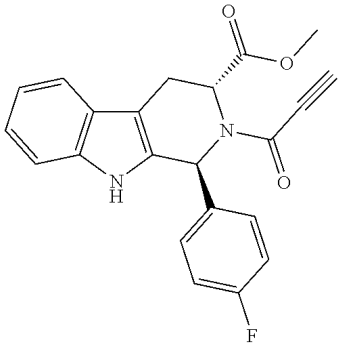


Compound 144



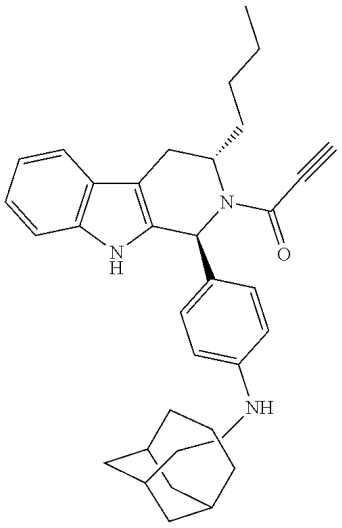
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Compound 146



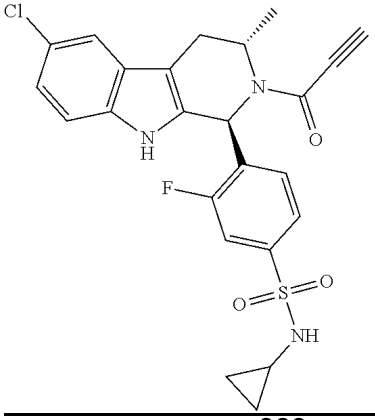
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Compound 148



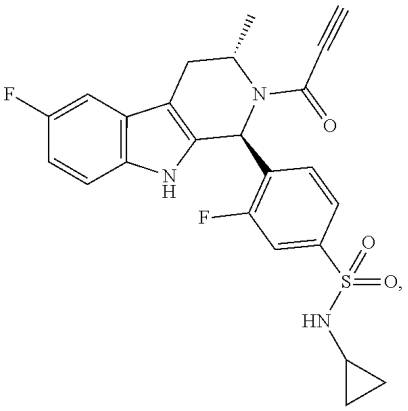
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Compound 151

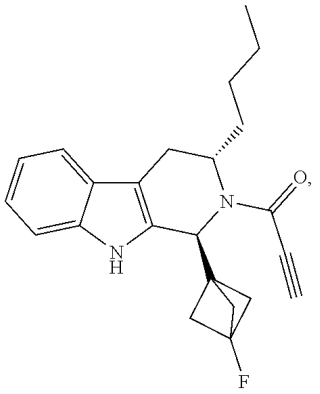


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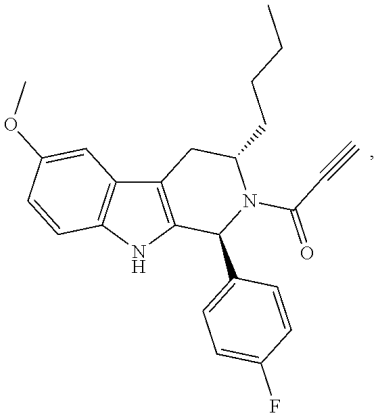
Compound 153



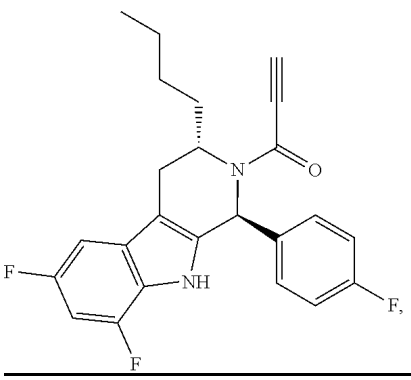
Compound 154



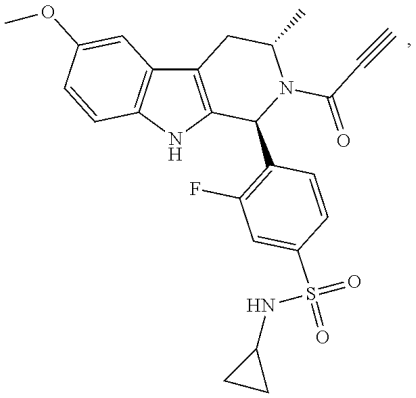
Compound 155



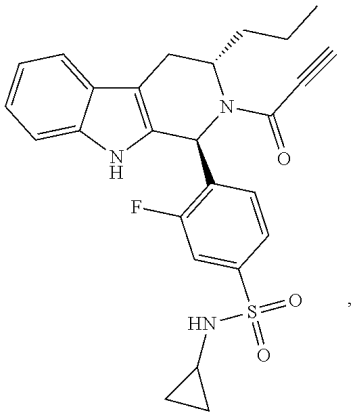
Compound 156



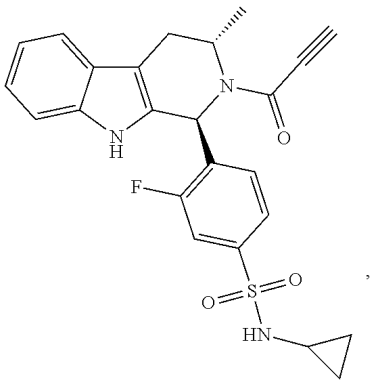
Compound 165



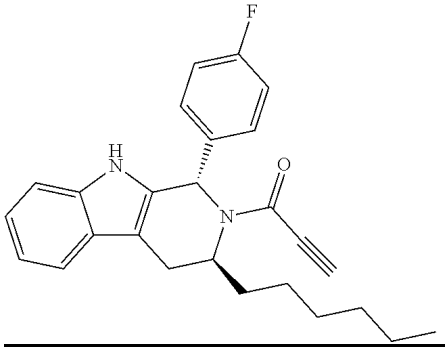
Compound 167



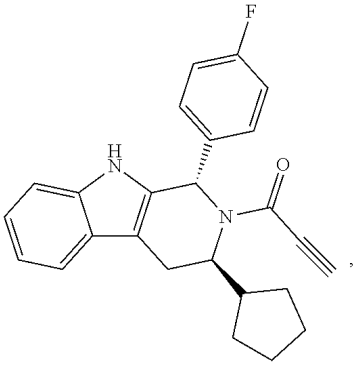
Compound 174



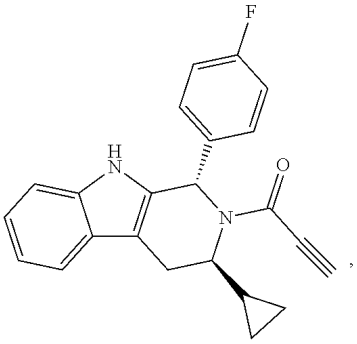
Compound 176



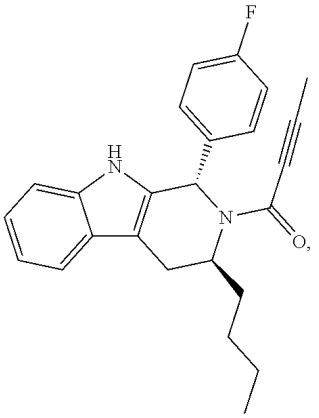
Compound 177



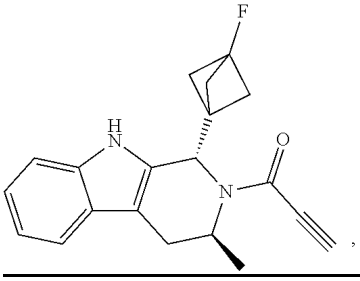
Compound 178



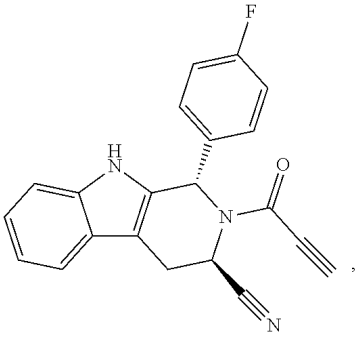
Compound 180



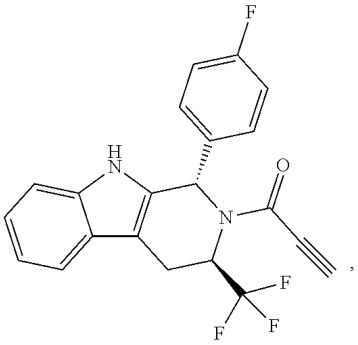
Compound 182



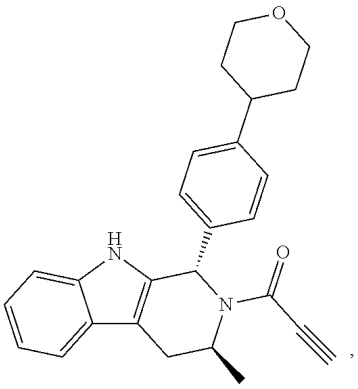
Compound 190



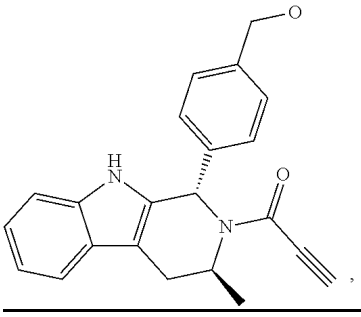
Compound 191



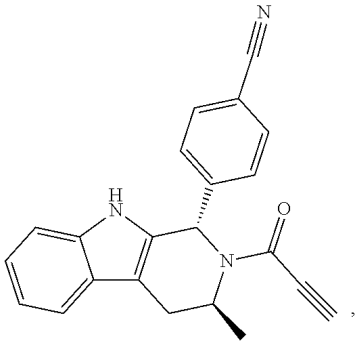
Compound 192



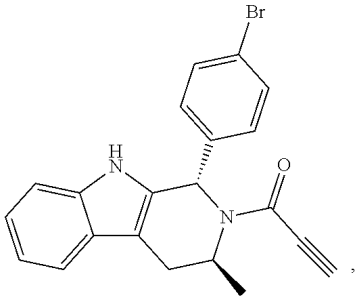
Compound 193



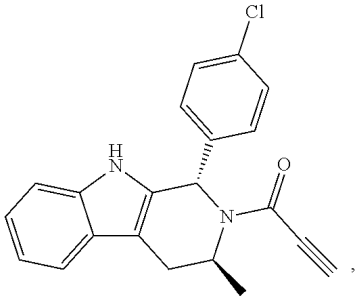
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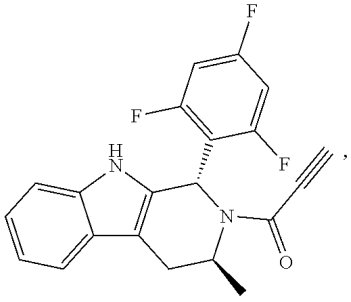
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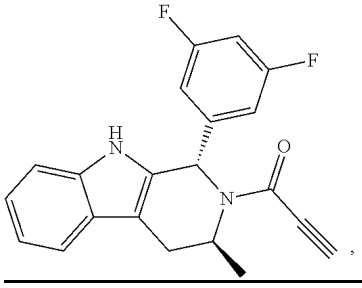
Compound 196



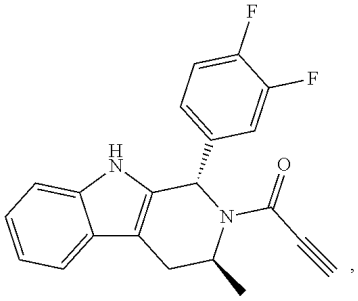
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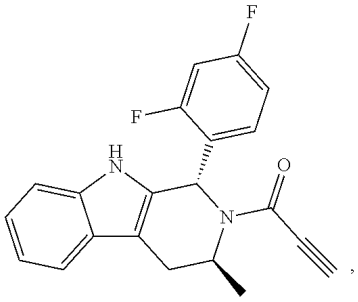
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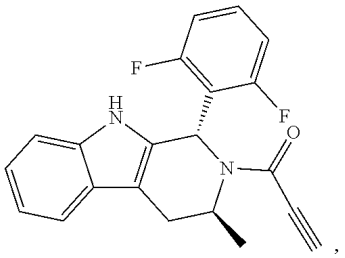
Compound 199



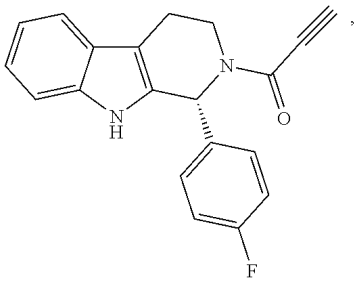
Compound 200



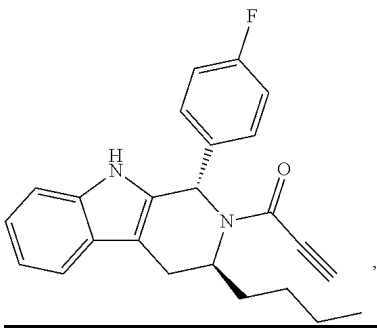
Compound 201



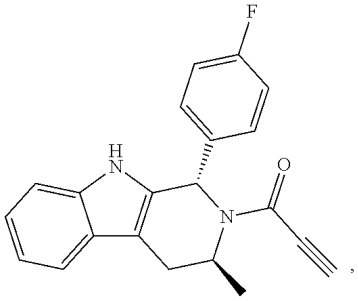
Compound 202



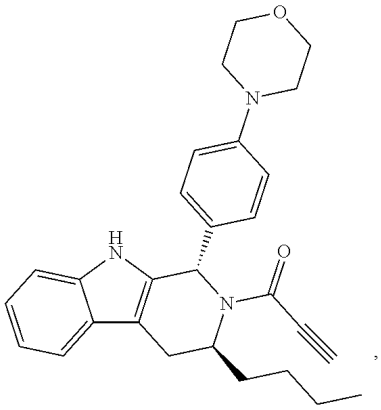
Compound 205



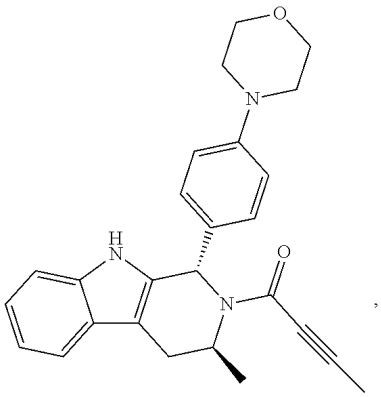
Compound 206



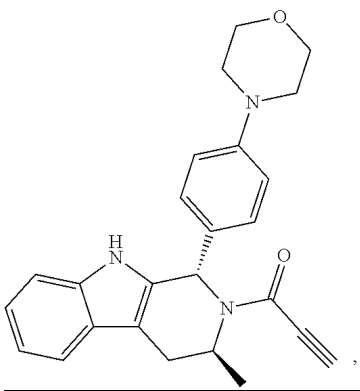
Compound 216



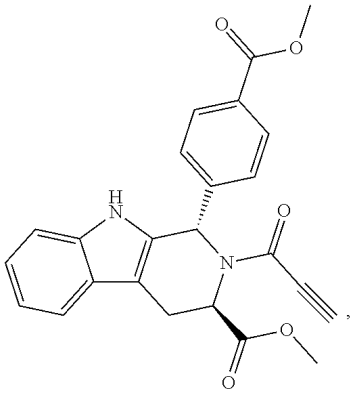
Compound 224



Compound 231

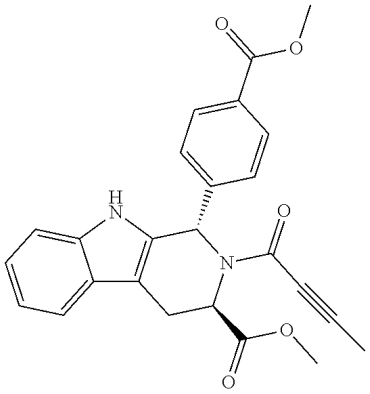


Compound 271



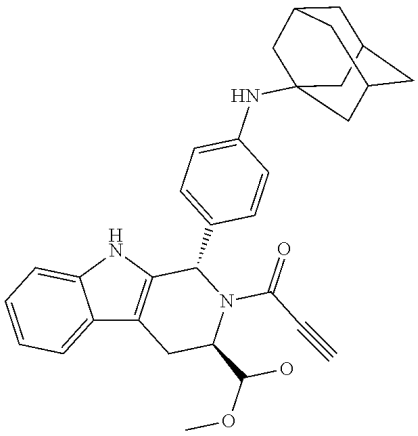
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Compound 272



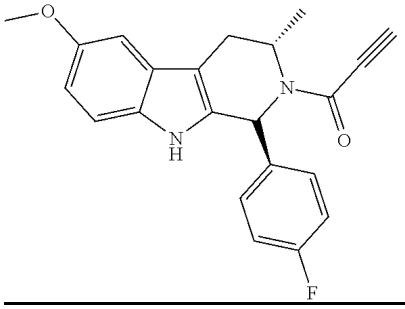
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Compound 275



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Compound 282



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