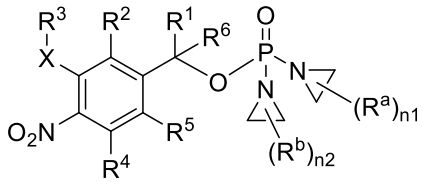
WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein:

(2) R^1 and R^2, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered carbocyclic or heterocyclic ring, and
R^4 and R^5 are as defined in (1); or

(3) R^1 and R^5, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered carbocyclic or heterocyclic ring; and
R^2 and R^4 are as defined in (1); or

(4) R^4 and R^5, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered ring; or
R^1 and R^2 are as defined in (1) or (2); or

(1) R^1 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl; and
R^2, R^4, and R^5 are each independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} alkoxy, or an optionally substituted 3-5 membered ring; and

wherein:

X is O, S, NR^{10}, an optionally substituted C_{1-4} alkylene, or an optionally substituted C_{1-4} heteroalkylene, wherein R^{10} is hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted 3-6 membered ring, or a nitrogen protecting group;

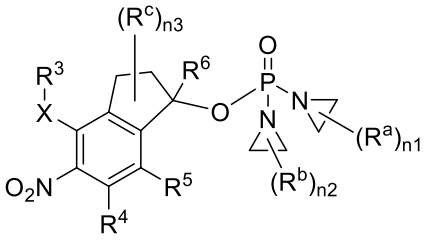
R^3 is hydrogen, an optionally substituted C_{1-4} alkyl, or an optionally substituted 3-10 membered ring;

R^6 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

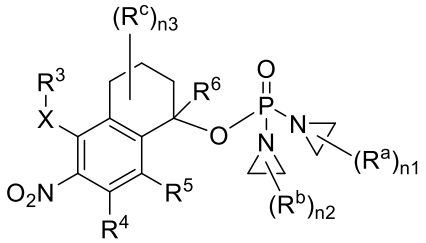
the integers n1 and n2 are each independently 0, 1, 2, 3, or 4;

each of R^a and R^b at each occurrence is independently an optionally substituted C_{1-4} alkyl or an optionally substituted C_{1-4} heteroalkylene; or two instances of R^a or two instances of R^b, together with the intervening atom(s), are joined together to form an optionally substituted 3-6 membered ring, and any remaining instances of R^a and/or R^b are as defined above.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula I-1, I-2, I-3, I-1-B-E1, I-1-B-E2, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, or I-12:



Formula I-1,



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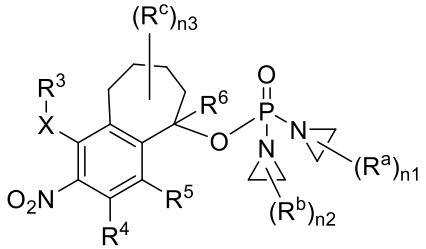

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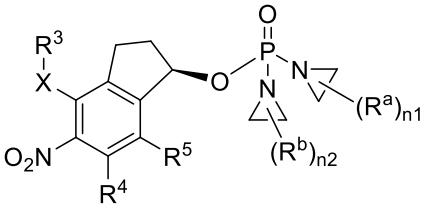
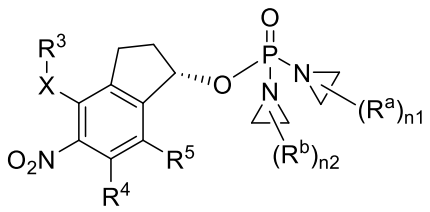


Formula I-1-B-E1,



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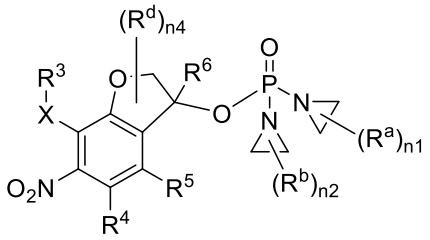

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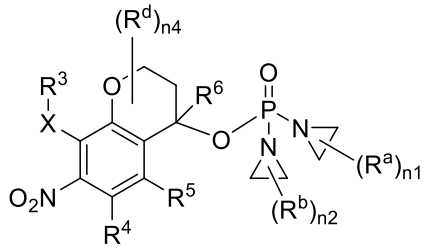

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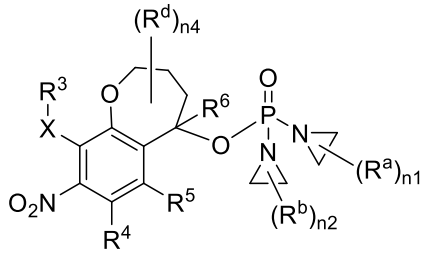

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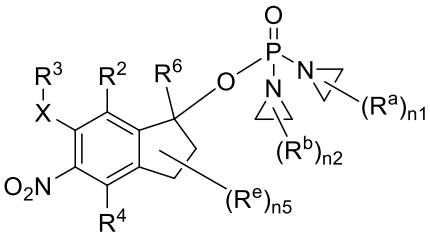

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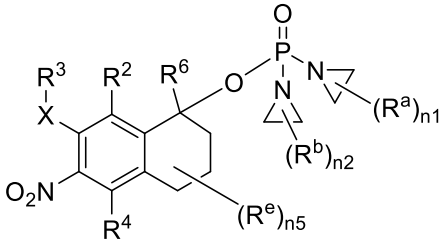

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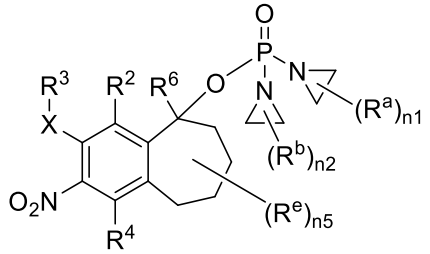

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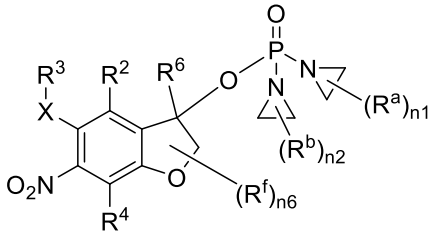

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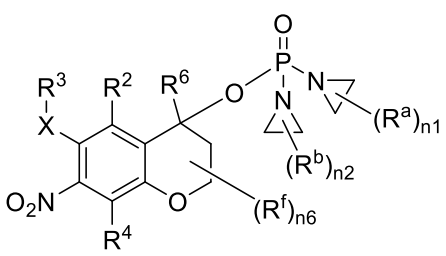
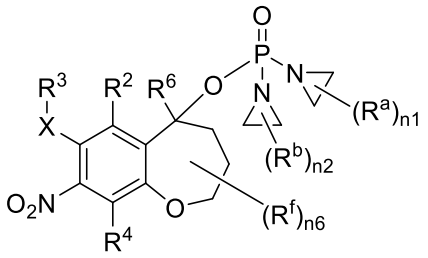


Formula I-11, or



Formula I-12,

wherein:

the integer n3 is 0, 1, or 2; and

R^c at each occurrence is independently oxo, F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having one or two heteroatoms and optionally substituted with F; or two instances of R^c are joined with the intervening atom(s) to form an optionally substituted 3-6 membered ring;

the integer n4 is 0, 1, or 2; and

R^d at each occurrence is independently oxo, F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having one or two heteroatoms and optionally substituted with F; or two instances of R^d are joined with the intervening atom(s) to form an optionally substituted 3-6 membered ring;

the integer n5 is 0, 1, or 2; and

R^e at each occurrence is independently oxo, F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having one or two heteroatoms and optionally substituted with F; or two instances of R^e are joined with the intervening atom(s) to form an optionally substituted 3-6 membered ring;

the integer n6 is 0, 1, or 2; and

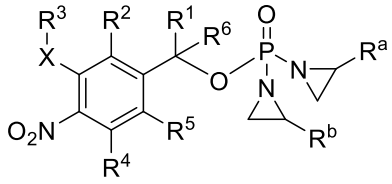
R^f at each occurrence is independently oxo, F, OH, NH_2, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having one or two heteroatoms and optionally

substituted with F; or two instances of R^f are joined with the intervening atom(s) to form an optionally substituted 3-6 membered ring.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein n3 is 0, n4 is 0, n5 is 0, or n6 is 0.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein both n1 and n2 are 0; or

wherein the compound is characterized as having a structure according to Formula I-13:



Formula I-13.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen, deuterium, CH_3, or CF_3;

wherein R^4 is hydrogen;

wherein as applicable, R^5 is hydrogen;

wherein as applicable, R^2 is hydrogen;

wherein as applicable, R^1 is hydrogen, deuterium, or C_{1-4} alkyl optionally substituted with F; and/or

wherein X is O.

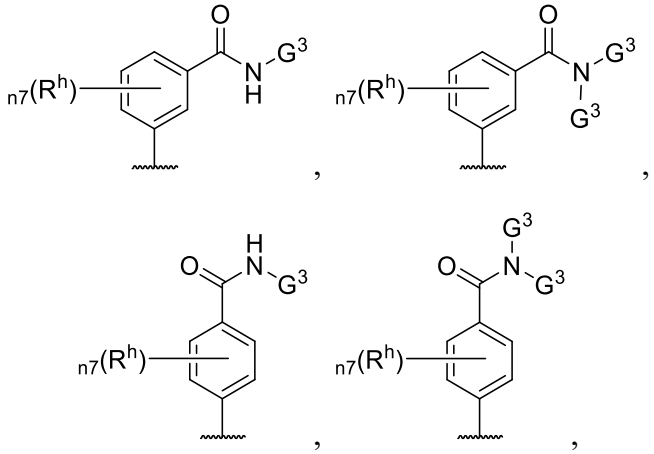
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is an optionally substituted phenyl, an optionally substituted 5 or 6-membered heteroaryl, or an optionally substituted bicyclic heteroaryl;

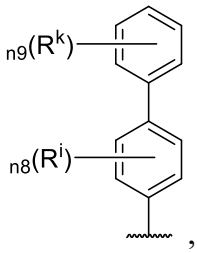
wherein R^3 is a phenyl which is substituted with 1-3 substituents each independently selected from halogen, CN, OH, NH_2, COOH, $CONH_2$, G^1, OG^1, SG^1, NHG^1, NG^1G^1, $C(O)G^1$, $COOG^1$, $CONHG^1$, $CONG^1G^1$, $OC(O)G^1$, $OCOOG^1$, $OCONHG^1$,

$OCONG^1G^1$, $NHC(O)G^1$, $NHCOOG^1$, $NHCONHG^1$, $NHCONG^1G^1$, $NG^1C(O)G^1$, NG^1COOG^1, NG^1CONHG^1, $NG^1CONG^1G^1$, SO_2G^1, SO_2NHG^1, or $SO_2NG^1G^1$, wherein G^1 at each occurrence is independently an optionally substituted C_{1-4} alkyl, an optionally substituted C_{2-4} alkenyl, an optionally substituted C_{2-4} alkynyl, or an optionally substituted 3-6 membered ring structure, or two G^1 of an NG^1G^1 can join together with the nitrogen atom to form an optionally substituted 4-8 membered heterocyclic ring; or

wherein R^3 is a phenyl which is substituted with 1-3 substituents each independently selected from F, Cl, CN, OH, NH_2, COOH, $CONH_2$, G^2, OG^2, NHG^2, NG^2G^2, $C(O)G^2$, $COOG^2$, $CONHG^2$, $CONG^2G^2$, SO_2G^2, SO_2NHG^2, or $SO_2NG^2G^2$, wherein G^2 at each occurrence is independently a C_{1-4} alkyl, C_{3-6} cycloalkyl, 3-6 membered heterocyclic ring having 1-2 ring heteroatoms, phenyl, or 5 or 6-membered heteroaryl, each of which is optionally substituted with 1-3 substituents independently selected from F, Cl, OH, NH_2, C_{1-4} alkyl optionally substituted with 1-3 F, or C_{1-4} heteroalkyl having 1 or 2 heteroatoms and optionally substituted with 1-3 F, or two G^2 of an NG^2G^2 can join together with the nitrogen atom to form an optionally substituted 4-8 membered heterocyclic ring having 0 or 1 additional ring heteroatom.

7. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^3 is:





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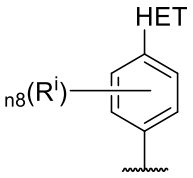

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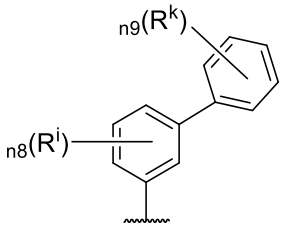

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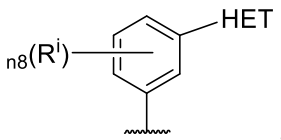

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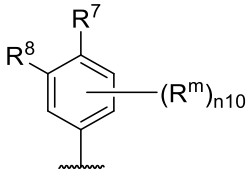

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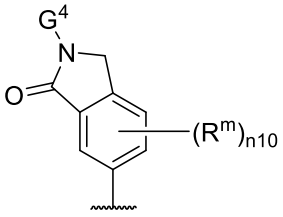

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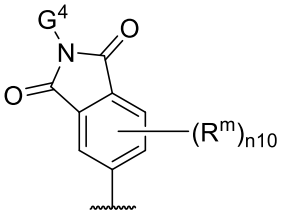

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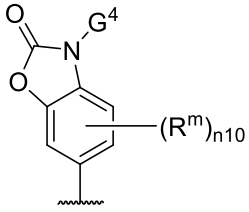

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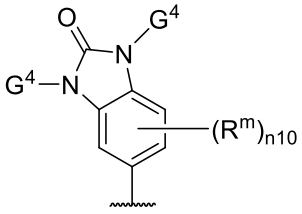

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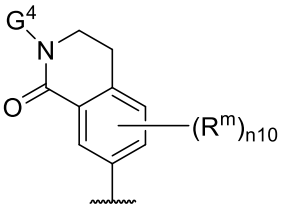

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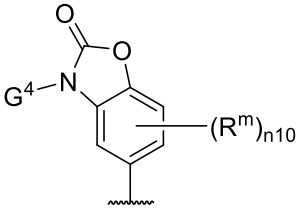

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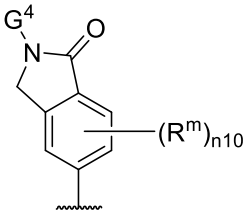

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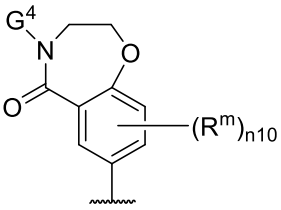

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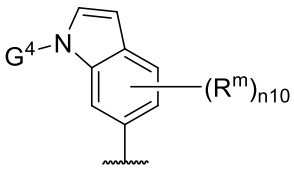

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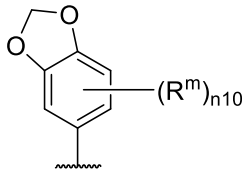


,

wherein:

G^3 at each occurrence is independently an optionally substituted C_{1-4} alkyl or optionally substituted 3-6 membered ring, or a deuterated analog of the C_{1-4} alkyl or 3-6 membered ring, when substituted, the C_{1-4} alkyl or 3-6 membered ring is substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F, or 3-6 membered ring optionally substituted with F; or

two G^3 together with the nitrogen atom they are both attached to are joined to form a 4-8 membered heterocyclic ring having 0 or 1 additional ring heteroatom, wherein the 4-8 membered heterocyclic ring is optionally substituted with 1-3 substituents each independently oxo, F, C_{1-4} alkyl, OH, NH_2, or C_{1-4} heteroalkyl having 1-2 heteroatoms; and wherein:

the integer n7 is 0, 1, or 2; and

R^h at each occurrence is independently a halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring is optionally substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

the integers n8 and n9 are independently 0, 1, or 2;

HET is a 5 or 6 membered heteroaryl optionally substituted with 1-2 R^j; and

each of R^i, R^j, and R^k at each occurrence is independently a halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring is optionally substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F or OH, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

the integer n10 is 0, 1, or 2; and

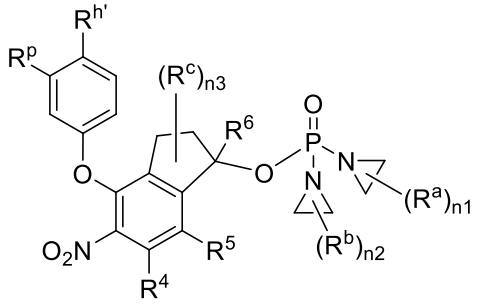
R^7 and R^8, together with the intervening atoms, are joined to form a 4-8 membered ring, which is optionally substituted with 1-3 R^n; and

R^m at each occurrence is independently a halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring is optionally substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F; and

R^n at each occurrence is independently oxo (as valency permits), halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring is optionally substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F; and

G^4 at each occurrence is independently an optionally substituted C_{1-4} alkyl, or optionally substituted 3-6 membered ring, when substituted, the C_{1-4} alkyl or 3-6 membered ring is substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F.

8. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, characterized as having a structure according to Formula IV-1, IV-7, IV-8, IV-2, IV-3, IV-4, IV-5, or IV-6:



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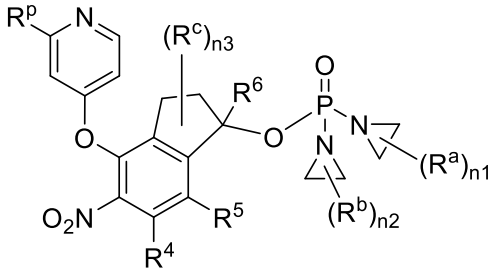

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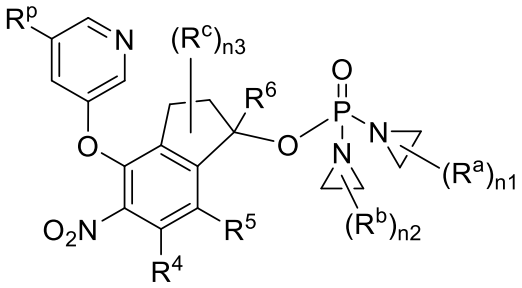

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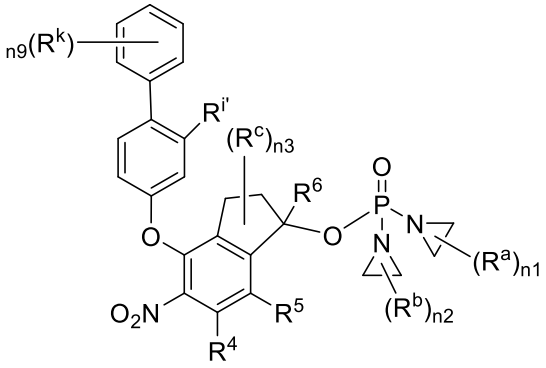
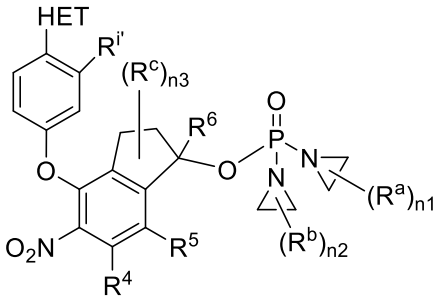
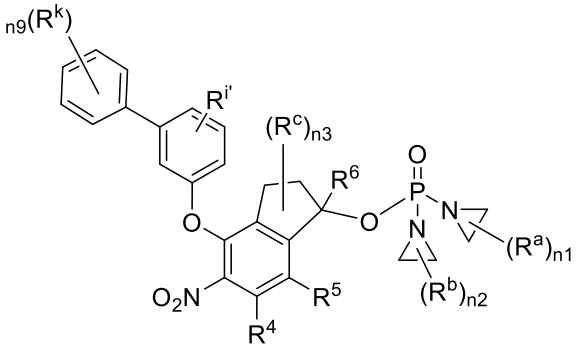


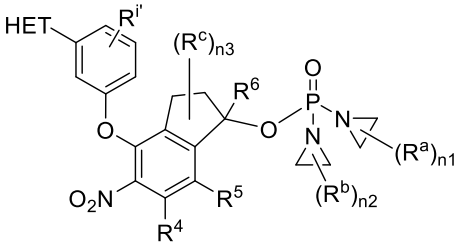
Formula IV-2,

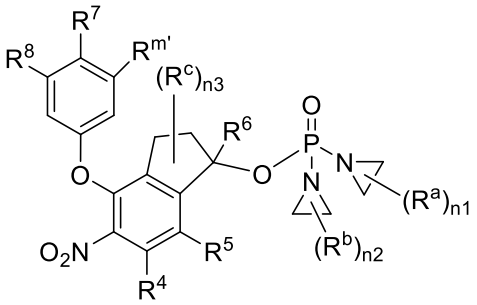




Formula IV-3,

Formula IV-4,





Formula IV-5, or

Formula IV-6,

wherein:

R^p is halogen, CN, OH, NH_2, COOH, $CONH_2$, G^3, OG^3, SG^3, NHG^3, NG^3G^3, $C(O)G^3$, $COOG^3$, $CONHG^3$, $CONG^3G^3$, $OC(O)G^3$, $OCOOG^3$, $OCONHG^3$, $OCONG^3G^3$, $NHC(O)G^3$, $NHCOOG^3$, $NHCONHG^3$, $NHCONG^3G^3$, $NG^3C(O)G^3$, NG^3COOG^3, NG^3CONHG^3, $NG^3CONG^3G^3$, SO_2G^3, SO_2NHG^3, or $SO_2NG^3G^3$,

G^3 at each occurrence is independently an optionally substituted C_{1-4} alkyl or optionally substituted 3-6 membered ring, or a deuterated analog of the C_{1-4} alkyl or 3-6 membered ring, when substituted, the C_{1-4} alkyl or 3-6 membered ring is substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F, or 3-6 membered ring optionally substituted with F; or

two G^3 together with the nitrogen atom they are both attached to are joined to form a 4-8 membered heterocyclic ring having 0 or 1 additional ring heteroatom, wherein the 4-8

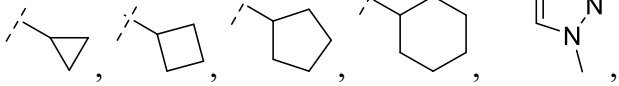
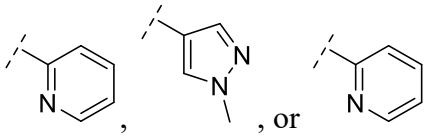
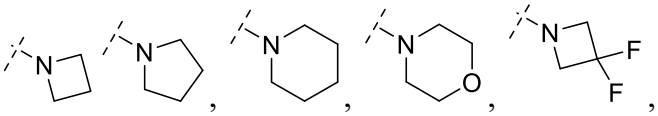
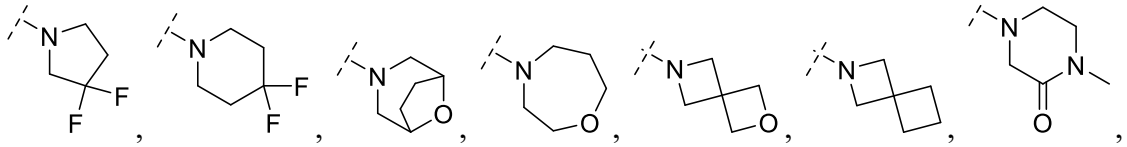
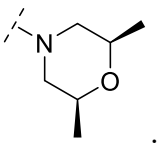
membered heterocyclic ring is optionally substituted with 1-3 substituents each independently oxo, F, C_{1-4} alkyl, OH, NH_2, or C_{1-4} heteroalkyl having 1-2 heteroatoms;

$R^{h'}$ is hydrogen or R^h; and

R^h at each occurrence is independently a halogen, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, or a 3-6 membered ring, wherein the C_{1-4} alkyl, C_{1-4} alkoxy, or 3-6 membered ring is optionally substituted with 1-3 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

wherein $R^{i'}$ is hydrogen or R^i; and

wherein $R^{m'}$ is hydrogen or R^m.

9. The compound of claim 7 or 8, or a pharmaceutically acceptable salt thereof, wherein each G^3 is independently methyl, , , or ; or two G^3 together with the nitrogen atom they are both attached to are joined to form , , or .

10. The compound of any one of claims 7 to 9, or a pharmaceutically acceptable salt thereof, wherein n7 is 0, or $R^{h'}$ is hydrogen;

wherein n7 is 1, and R^h is a halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or a 3-6 membered ring optionally substituted with 1-2 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

wherein n8 is 0, or $R^{i'}$ is hydrogen;

wherein n8 is 1 and R^i is a halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or a 3-6 membered ring optionally substituted with 1-2 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

wherein n9 is 0;

wherein n9 is 1 and R^k is a halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or a 3-6 membered ring optionally substituted with 1-2 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F;

wherein R^7 and R^8, together with the intervening atoms, are joined to form a 5 or 6 membered heteroaryl ring having 1-3 ring heteroatoms, which is optionally substituted with 1-2 R^n;

wherein R^7 and R^8, together with the intervening atoms, are joined to form a 4-7 membered heterocyclyl ring having 1 or 2 ring heteroatoms, which is optionally substituted with 1-2 R^n;

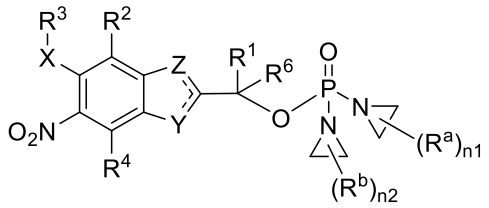
wherein n10 is 0, or $R^{m'}$ is hydrogen; or

wherein n10 is 1, and R^m is a halogen, CN, C_{1-4} alkyl optionally substituted with F, C_{1-4} alkoxy optionally substituted with F, or a 3-6 membered ring optionally substituted with

1-2 substituents each independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F.

11. The compound of any one of claims 7 to 10, or a pharmaceutically acceptable salt thereof, wherein HET is (1) a pyridyl, pyrimidinyl, pyrazinyl, pyridinonyl, or pyrimidinonyl, optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with F, or C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F; or (2) a pyrazole, oxadiazole, thiadiazole, triazole, tetrazole, thiazole, oxazole, or imidazole optionally substituted with 1-2 R^j, wherein R^j at each occurrence is independently F, OH, C_{1-4} alkyl optionally substituted with F, C_{1-4} heteroalkyl having 1-2 heteroatoms and optionally substituted with F or 3-4 membered ring.

12. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

X is O, S, NR^{10}, an optionally substituted C_{1-4} alkylene, or an optionally substituted C_{1-4} heteroalkylene, wherein R^{10} is hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted 3-6 membered ring, or a nitrogen protecting group;

Y and Z are each independently O, S, NR^{11} or CR^{12}, as valency permits, provided that the 5-membered ring containing Y and Z is aromatic; wherein:

(i) R^{11} is hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted 3-6 membered ring, or a nitrogen protecting group, R^{12} is hydrogen, halogen, CN, an optionally substituted C_{1-4} alkyl, an optionally substituted C_{1-4} heteroalkyl, or an optionally substituted 3-6 membered ring; or

(ii) R^{11} or R^{12}, as applicable, together with R^1 and the intervening atoms are joined together to form an optionally substituted 5-8 membered ring;

R^1 is defined in (ii) or is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

R^2 and R^4 are each independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4} alkynyl, optionally substituted C_{1-4} alkoxy, or an optionally substituted 3-5 membered ring;

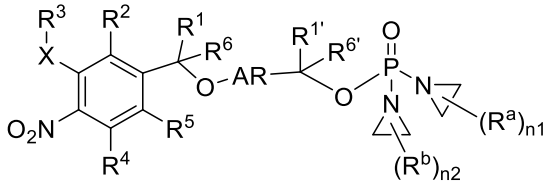
R^3 is hydrogen, an optionally substituted C_{1-4} alkyl, or an optionally substituted 3-10 membered ring;

R^6 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

the integers n1 and n2 are each independently 0, 1, 2, 3, or 4; and

each of R^a and R^b at each occurrence is independently an optionally substituted C_{1-4} alkyl or an optionally substituted C_{1-4} heteroalkylene; or two instances of R^a or two instances of R^b, together with the intervening atoms, are joined together to form an optionally substituted 3-6 membered ring, and any remaining instances of R^a and/or R^b are as defined above.

13. A compound of Formula III, or a pharmaceutically acceptable salt thereof:



Formula III

(1) R^1 is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl; and

R^2, R^4, and R^5 are each independently hydrogen, halogen, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, optionally substituted C_{2-4}

alkynyl, optionally substituted C_{1-4} alkoxy, or an optionally substituted 3-5 membered ring; or

(2) R^1 and R^2, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered carbocyclic or heterocyclic ring, and
R^4 and R^5 are as defined in (1); or

(3) R^1 and R^5, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered carbocyclic or heterocyclic ring; and
R^2 and R^4 are as defined in (1); or

(4) R^4 and R^5, together with the intervening atoms, are joined to form an optionally substituted 4-8 membered ring; and
R^1 and R^2 are as defined in (1) or (2); and

wherein:

X is O, S, NR^{10}, an optionally substituted C_{1-4} alkylene, or an optionally substituted C_{1-4} heteroalkylene, wherein R^{10} is hydrogen, an optionally substituted C_{1-4} alkyl, an optionally substituted 3-6 membered ring, or a nitrogen protecting group;

AR represents an optionally substituted arylene or optionally substituted heteroarylene;

R^3 is hydrogen, an optionally substituted C_{1-4} alkyl, or an optionally substituted 3-10 membered ring;

$R^{1'}$ is hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

R^6 and $R^{6'}$ are each independently hydrogen, deuterium, optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl, or optionally substituted C_{2-4} alkynyl;

the integers n1 and n2 are each independently 0, 1, 2, 3, or 4; and

each of R^a and R^b at each occurrence is independently an optionally substituted C_{1-4} alkyl or an optionally substituted C_{1-4} heteroalkylene; or two instances of R^a or two instances of R^b, together with the intervening atoms, are joined together to form an optionally substituted 3-6 membered ring, and any remaining instances of R^a and/or R^b are as defined above.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein the carbon connected to R^6 has S-configuration; or

wherein the carbon connected to R^6 has R-configuration.

15. A compound selected from Examples 1-569 or the compounds shown in Tables A1-A18 herein, a stereoisomer thereof, a deuterated analog thereof, or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. Use of the compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating cancer.

18. The use of claim 17, wherein the cancer is selected from the group consisting of a cancer of the adrenal gland, bone, brain, breast, bronchi, colon and/or rectum, gallbladder, head and neck, kidneys, larynx, liver, lung, neural tissue, pancreas, prostate, parathyroid, skin, stomach, and thyroid; and acute and chronic lymphocytic and granulocytic tumors, adenocarcinoma, adenoma, basal cell carcinoma, cervical dysplasia and in situ carcinoma, Ewing's sarcoma, epidermoid carcinomas, giant cell tumor, glioblastoma multiforma, hairy-cell tumor, intestinal ganglioneuroma, hyperplastic corneal nerve tumor, islet cell carcinoma, Kaposi's sarcoma, leiomyoma, leukemias, lymphomas, malignant carcinoid, malignant melanomas, malignant hypercalcemia, marfanoid habitus tumor, medullary carcinoma, metastatic skin carcinoma, mucosal neuroma, myeloma, mycosis fungoides, neuroblastoma, osteo sarcoma, osteogenic and other sarcoma, ovarian tumor, pheochromocytoma, polycythermia vera, primary brain tumor, small-cell lung tumor, squamous cell carcinoma of both ulcerating and papillary type, hyperplasia, seminoma, soft tissue

sarcoma, retinoblastoma, rhabdomyo sarcoma, renal cell tumor, topical skin lesion, veticulum cell sarcoma, and Wilm's tumor; particularly

wherein the cancer is liver cancer, non-small cell lung cancer, melanoma, renal cell carcinoma, or prostate cancer.

19. The use of claim 17 or 18, wherein the cancer is characterized as having abnormal AKR1C3 activity and/or overexpression of AKR1C3.