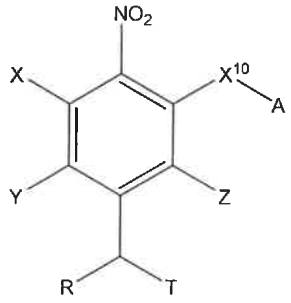
CLAIMS

1. A compound of formula I:



I

or a pharmaceutically acceptable salt, or a solvate of each thereof, wherein

X^{10} is O, S, SO, or SO_2;

A is $-N=CR^1R^2$;

each R^1 and R^2 independently is hydrogen, -CN, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-15 membered heterocycle, 5-15 membered heteroaryl, ether, $-CONR^{13}R^{14}$, or $-NR^{13}COR^{14}$, and at least one of R^1 and R^2 is -CN;

each X, Y, and Z independently is hydrogen, CN, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-15 membered heterocycle, 5-15 membered heteroaryl, ether, $-CONR^{13}R^{14}$, or $-NR^{13}COR^{14}$;

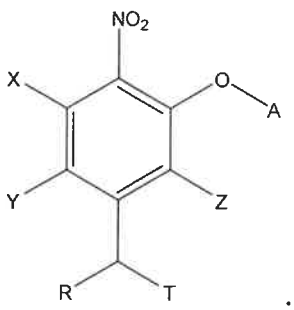
R is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-15 membered heterocycle, 5-15 membered heteroaryl, ether, $-CONR^{13}R^{14}$, or $-NR^{13}COR^{14}$;

each R^{13} and R^{14} independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-15 membered heterocycle, 5-15 membered heteroaryl, or ether

T comprises a phosphoramidate alkylating agent; and

wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycle, heteroaryl, ether groups are optionally substituted.

2. The compound of claim 1 of formula I-A:



I-A

wherein the remaining variables are defined as in claim 1 above.

3. The compound of claim 1 or 2, wherein T is $OP(Z^1)(NR^{30}CH_2CH_2Cl)_2$, $OP(Z^1)(NR^{30}CH_2CH_2Br)2$, $OP(Z^1)(NR^{30}{}_2)(N(CH_2CH_2X^1)_2)$, $OP(Z^1)(N(CH_2)_2)_2$, or $OP(Z^1)(N(CH_2CH_2Cl)_2)_2$, wherein each R^{30} independently is hydrogen or C_1-C_6 alkyl or 2 R^{30} groups together with the nitrogen atom they are bound to form 5-7 membered heterocyclyl group, Z^1 is O or S, and X^1 is Cl, Br, or OMs.

4. The compound of any one of claims 1-3, wherein T is $OP(Z^1)(NHCH_2CH_2Cl)_2$, $OP(Z^1)(NHCH_2CH_2Br)2$, $OP(Z^1)(NH_2)(N(CH_2CH_2X^1)_2)$, $OP(Z^1)(N(CH_2)_2)_2$, or $OP(Z^1)(N(CH_2CH_2Cl)_2)_2$, wherein X^1 is defined as in claim 3.

5. The compound of any one of claims 1-4, wherein Z^1 is O.

6. The compound of any one of claims 1-5, wherein T is $OP(O)(N(CH_2CH_2))_2$, $OP(O)(NHCH_2CH_2Cl)_2$, $OP(O)(NHCH_2CH_2Br)_2$, or $OP(O)(NH_2)(N(CH_2CH_2Cl)_2)$.

7. The compound of any one of claims 1-6, wherein Z is hydrogen.

8. The compound of any one of claims 1-7, wherein X is hydrogen.

9. The compound of any one of claims 1-8, wherein Y is hydrogen or halo.

10. The compound of any one of claims 1-9, wherein R is hydrogen.

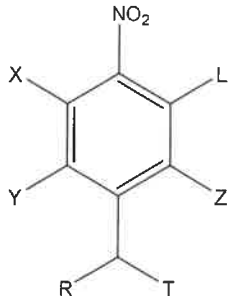
11. The compound of any one of claims 1-9, wherein R is C_1-C_6 alkyl.

12. The compound of any one of claims 1-9 and 11, wherein R is methyl.

13. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-12 and at least a pharmaceutically acceptable excipient or carrier.

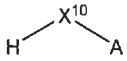
14. Use of the compound of any one of claims 1-12 or the composition of claim 13 in the meanufacture of a medicament for the treatment of cancer.

15. A process of making the compound of formula I of claim 1 comprising contacting a compound of formula II:



II

wherein L is a leaving group, and the remaining variables are defined as in claim 1, with a compound of formula III:



III

wherein X^{10} is defined as in claim 1, and optionally a base, to provide a compound of formula I.

16. Use of the compound of any one of claims 1-12 or the composition of claim 13 in the manufacture of a medicament for the treatment of cancer in a patient, wherein a AKR1C3 reductase level of the cancer is equal to or greater than a predetermined value.

17. Use of claim 16, wherein the AKR1C3 reductase level of the cancer is an intratumoral AKR1C3 reductase level of the cancer in a sample isolated from the patient.

18. A kit comprising a means for isolating a sample from a patient and determining an intratumoral AKR1C3 reductase level of the cancer in the sample using an AKR1C3 antibody; and a means for determining whether a compound of any one of claims 1-12 or a composition of claim 13 should be administered.