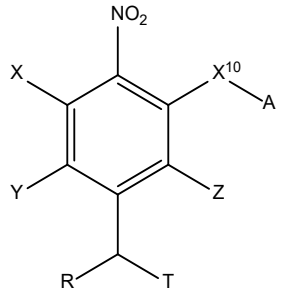
CLAIMS

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 C_6-C_{10} aryl, 5-15 membered heteroaryl, or -N=CR^1R^2;

R^1 is C_1-C_6 alkyl or CN and R^2 is C_6-C_{10} aryl~~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~~;

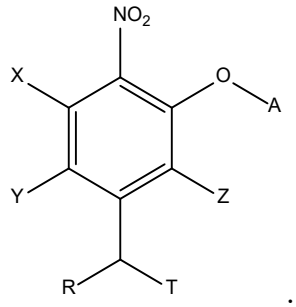
each X, Y, and Z independently is hydrogen, CN, halo, or C_1-C_6 alkyl~~, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-15 membered heterocycle, 5-15 membered heteroaryl, ether, -CONR^{13}R^{14}, or -NR^{13}COR^{14}~~;

R is hydrogen, or 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 is an -O-P(Z^1)(Z^5-X^5-Y^5)$_2$, where Z^5 is -NH, S or O, X^5 is optionally substituted ethylene, Y^5 is halo or -OSO_2-R^{20}, wherein R^{20} is optionally substituted alkyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, or Z^5-X^5-Y^5 is an aziridinyl (NCH_2CH_2) moiety; or 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)$_2$)$_2$ where each R^{30} 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 and X^1 is Cl, Br, or -OSO_2Me; and Z^1 is O or S~~comprises a phosphoramidate alkylating agent~~; and

wherein the alkyl, ~~alkenyl, alkynyl, cycloalkyl,~~ aryl, and ~~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 -OSO_2Me ~~-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 A is optionally substituted C_6-C_{10} aryl.

11. The compound of any one of claims 1-10, wherein A is optionally substituted phenyl.

12. The compound of any one of claims 1-9, wherein A is optionally substituted 5-15 membered heteroaryl.

13. The compound of any one of claims 1-9 and 12, wherein A is optionally substituted pyridyl.

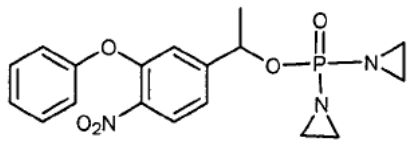
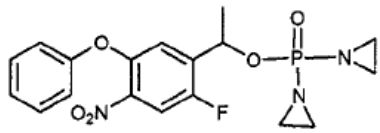
14. The compound of any one of claims 1-9, wherein A is -N=CR^{1}R^2 where R^1 and R^2 are defined as in claim 1.

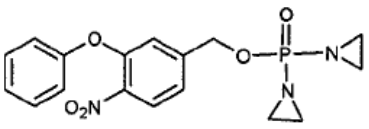
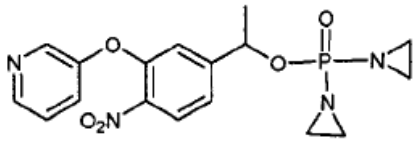
~~10.~~15. The compound of any one of claims 1-~~9~~14, wherein R is hydrogen.

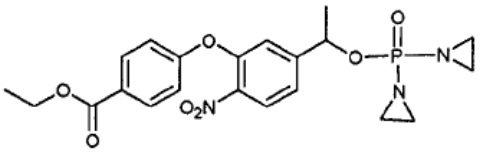
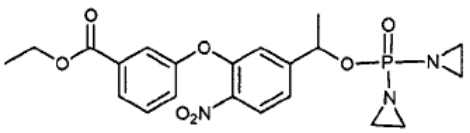
~~11.~~16. The compound of any one of claims 1-~~9~~14, wherein R is C_1-C_6 alkyl.

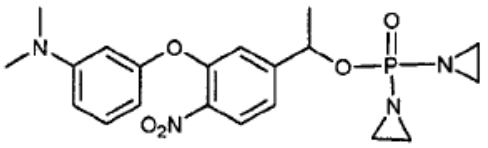
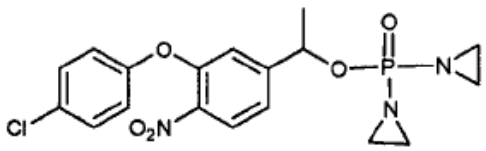
~~12.~~17. The compound of any one of claims 1-~~9~~14 and ~~11~~16, wherein R is methyl.

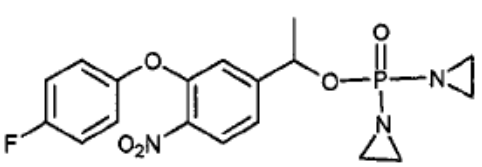
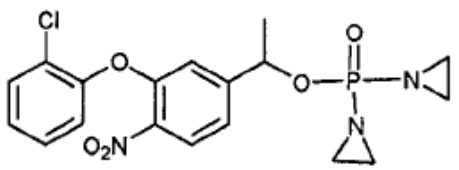
18. The compound of claim 1, wherein the compound is selected from the following compounds:

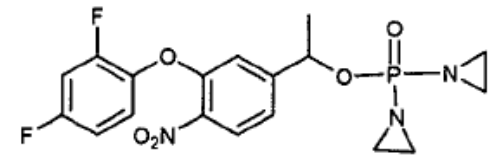
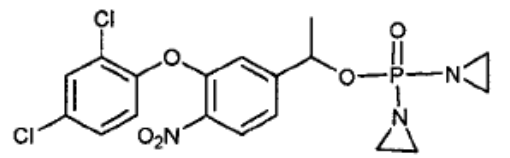
 ,  ,

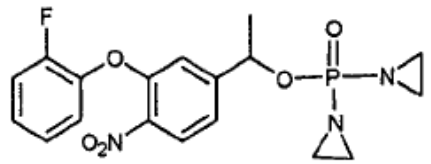
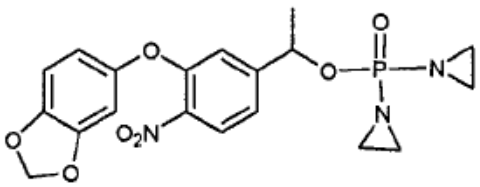
 ,  ,

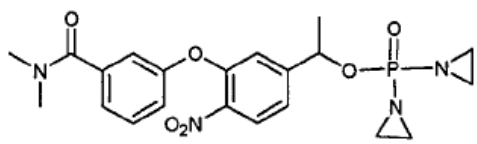
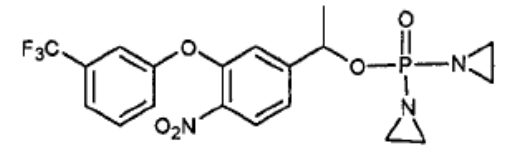
 ,  ,

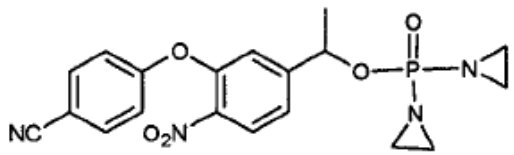
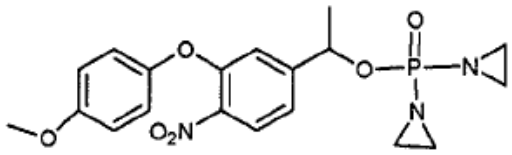
 ,  ,

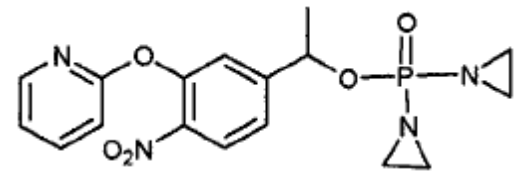
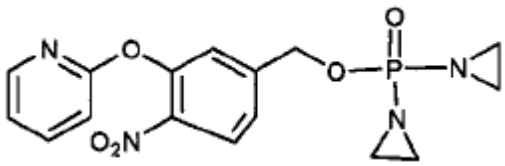
 ,  ,

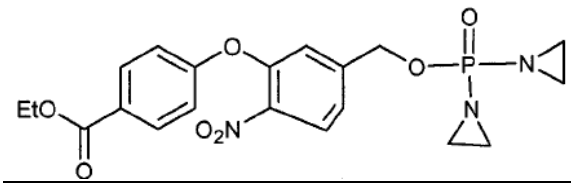
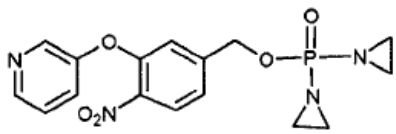
 ,  ,

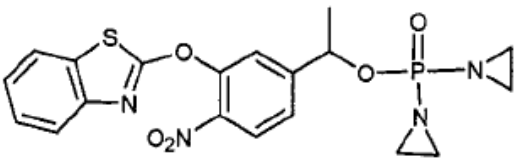
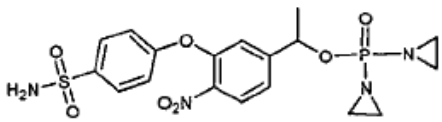
 ,  ,

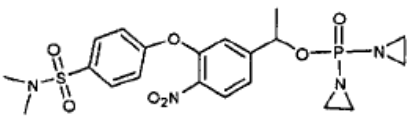
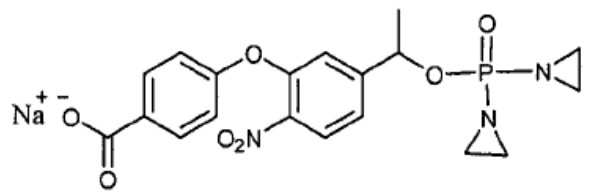
 ,  ,

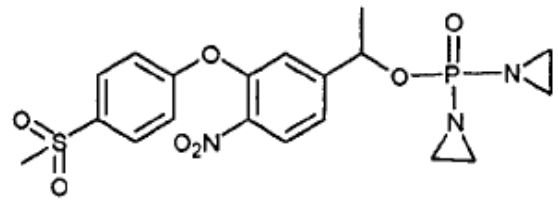
 ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,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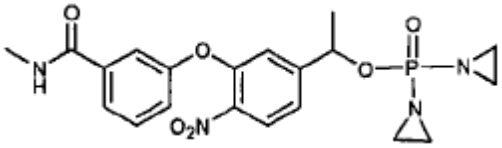
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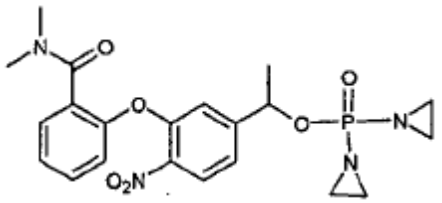
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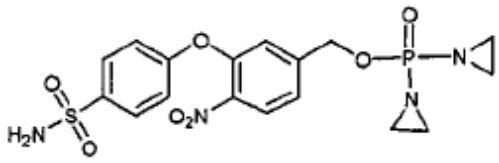
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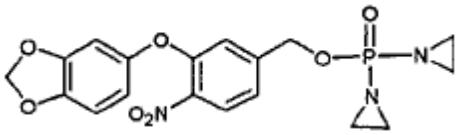
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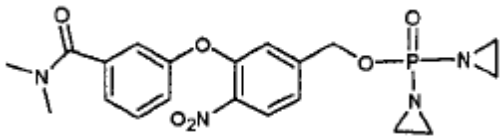
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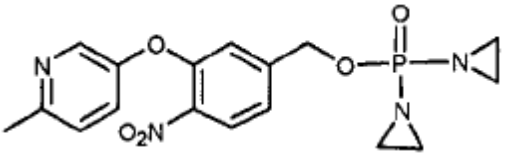
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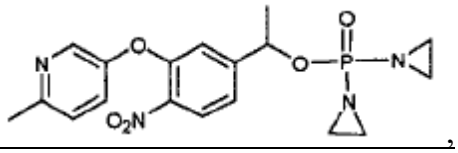
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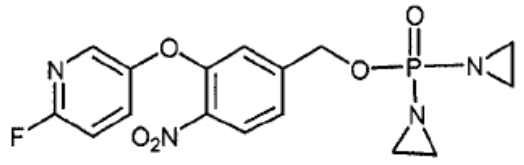
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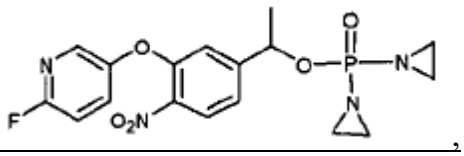
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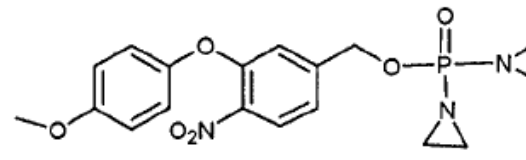
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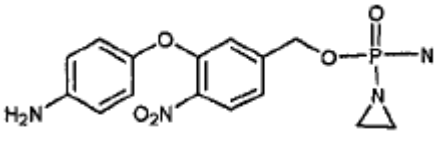
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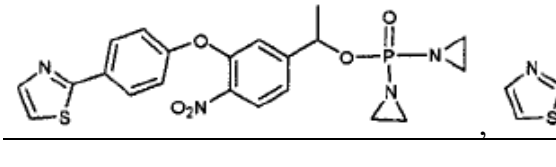
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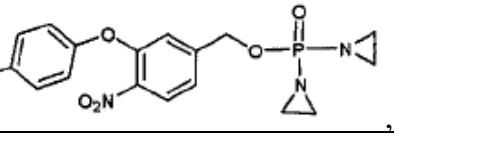
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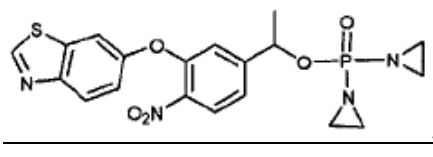
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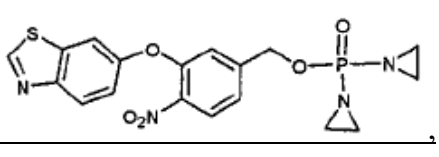
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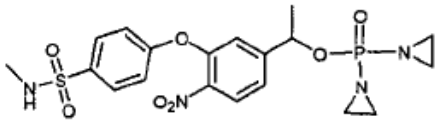
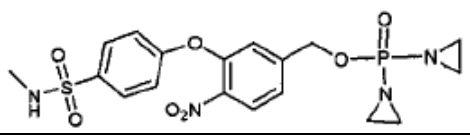
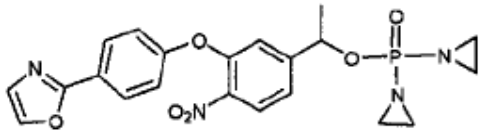
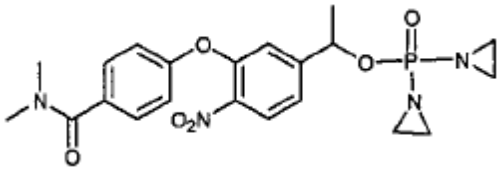
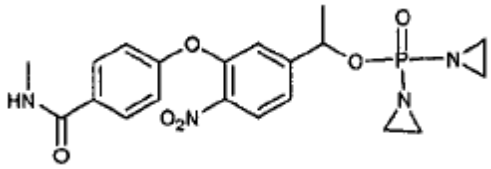
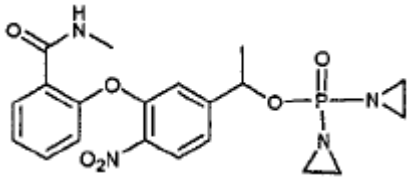
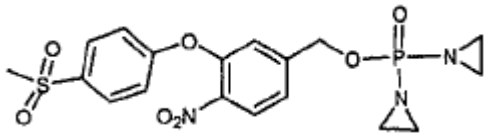
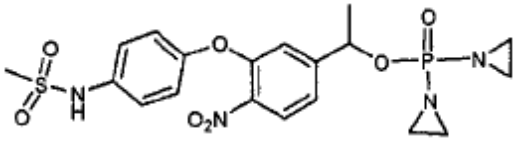
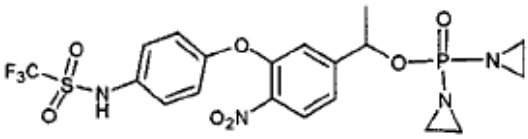
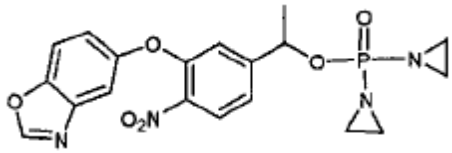
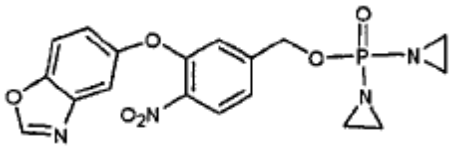
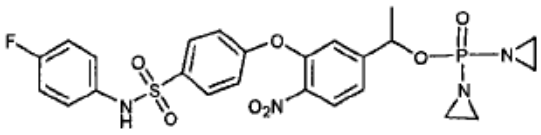
 ,  ,

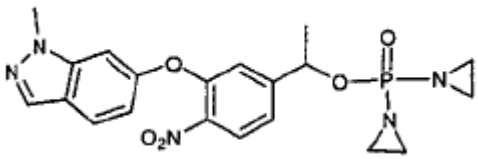
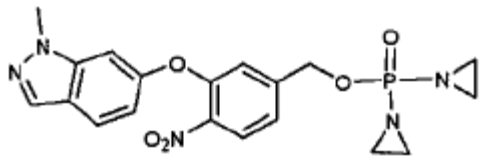
 ,  ,

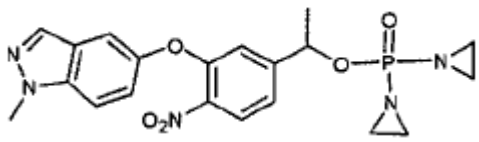
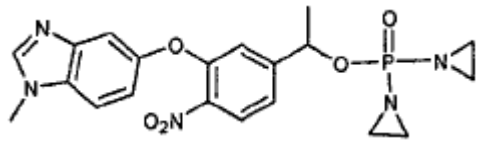
 ,  ,

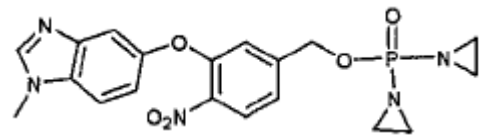
 ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,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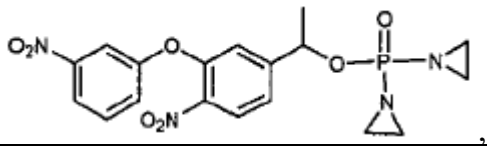
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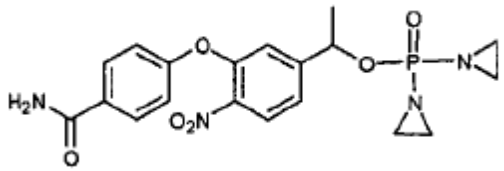
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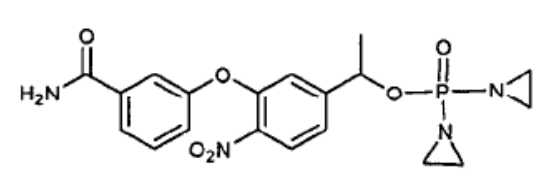
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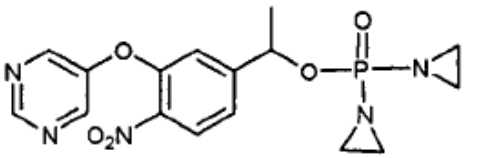
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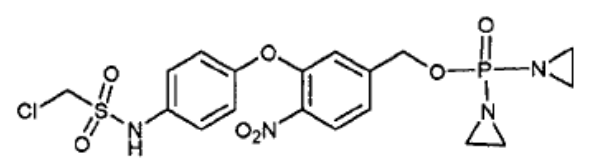
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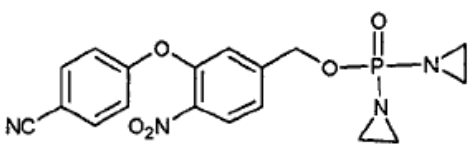
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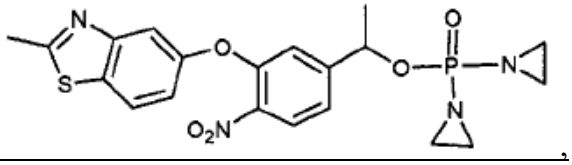
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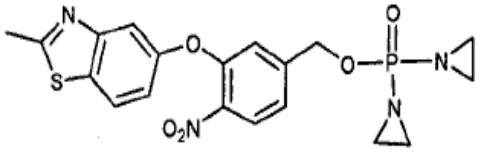
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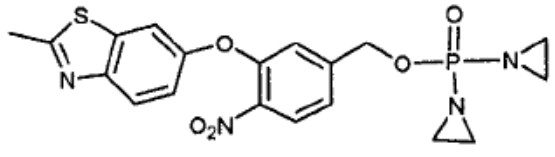
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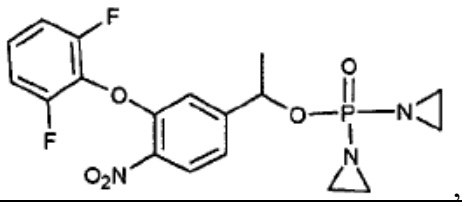
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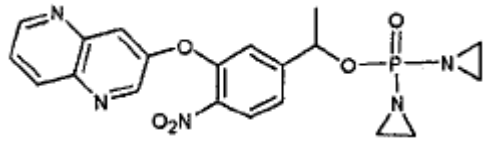
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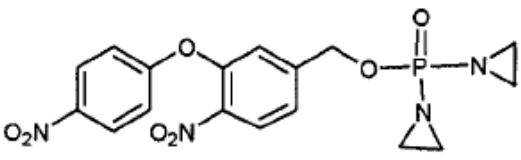
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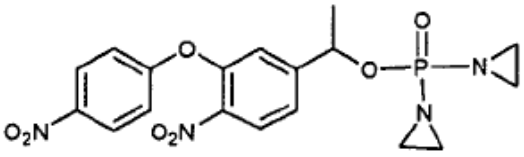
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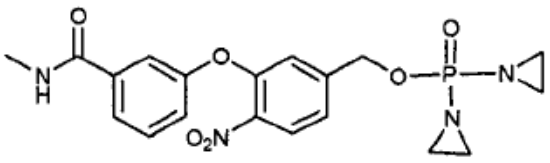
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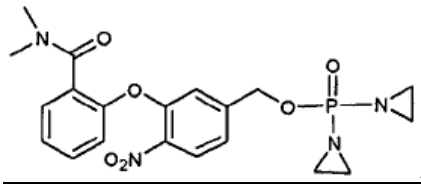
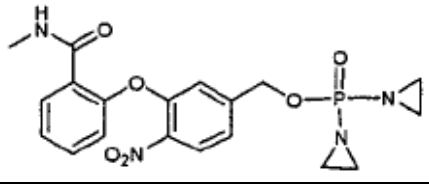
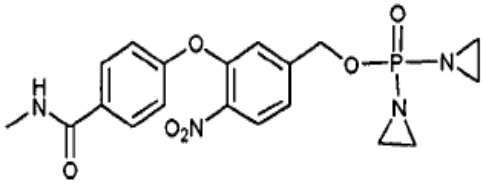
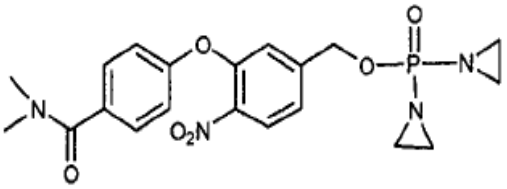
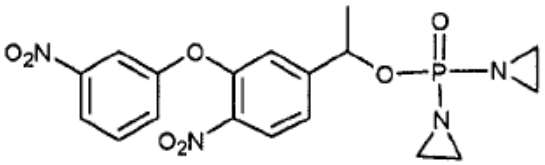
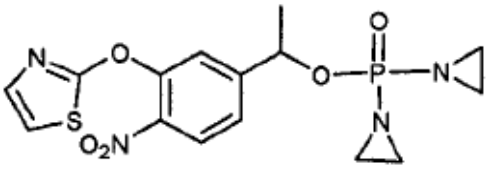
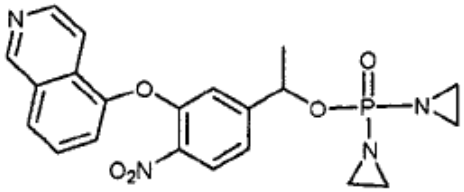
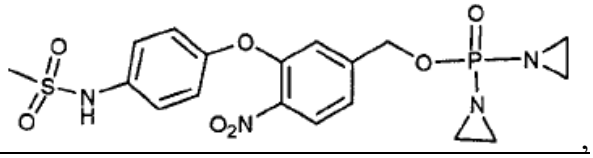
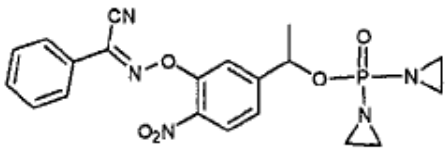
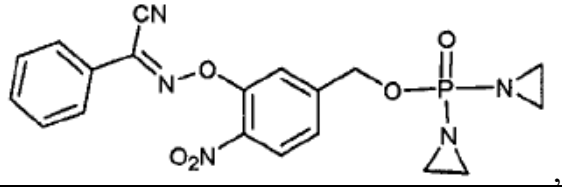
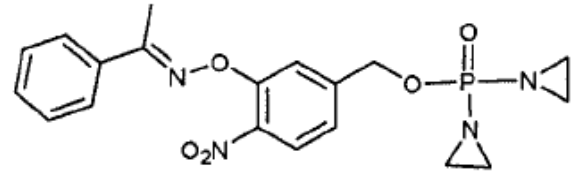
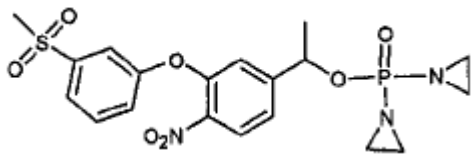
 ,  ,

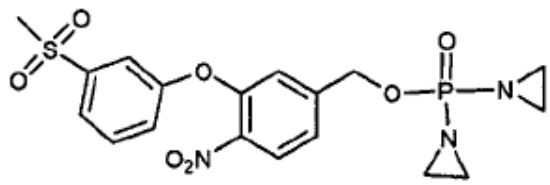
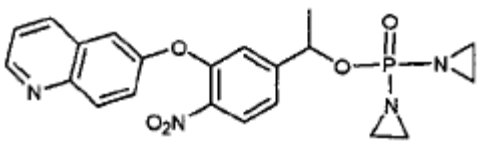
 ,  ,

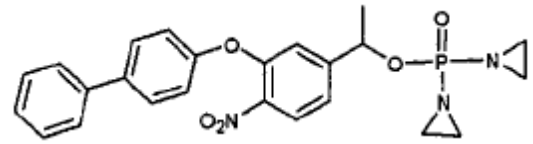
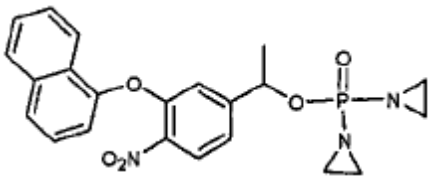
 ,  ,

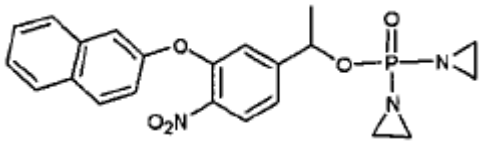
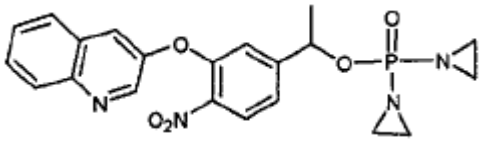
 ,  ,

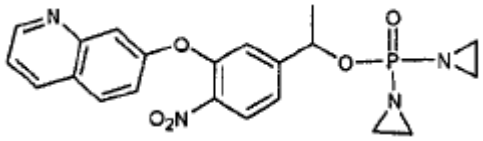
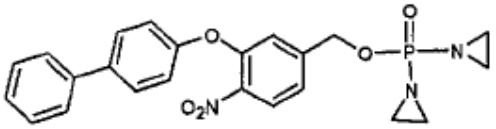
 ,  ,

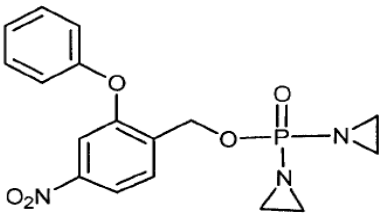
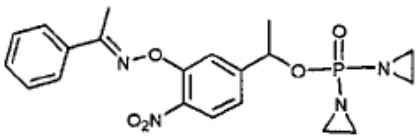
 ,  ,

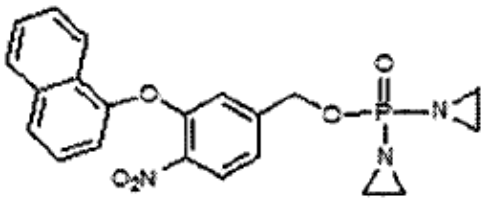
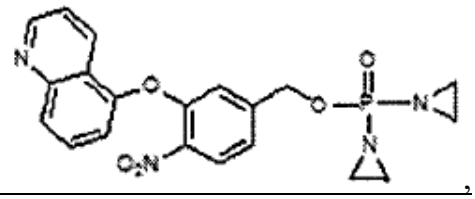
 ,  ,

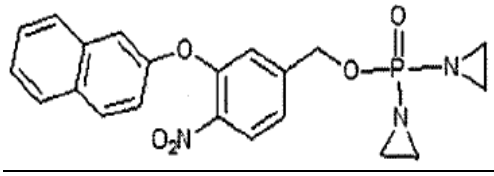
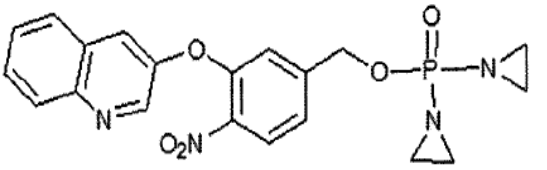
 ,  ,

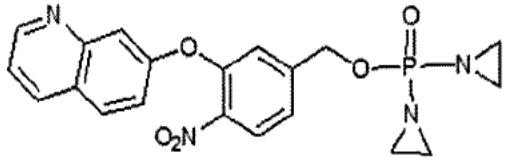
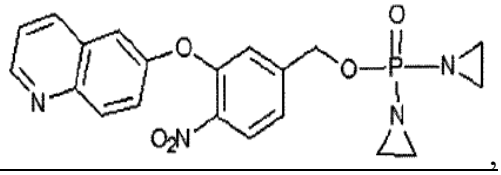
 ,  ,

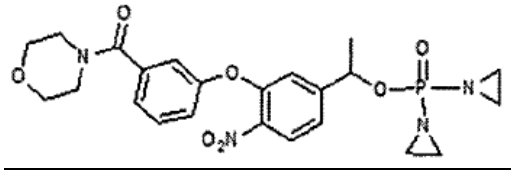
 ,  ,

 ,  ,

 ,  ,

 ,  ,

 ,  ,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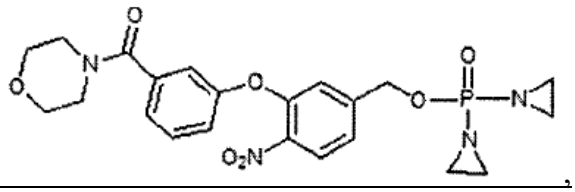
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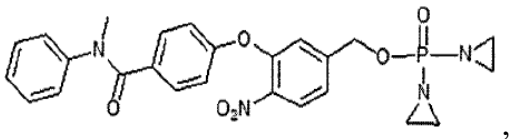
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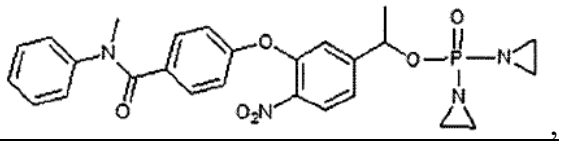
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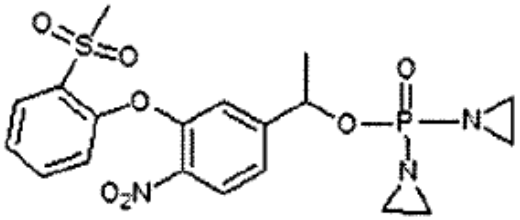
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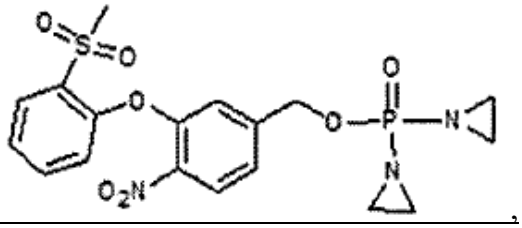
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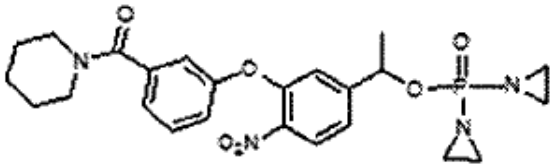
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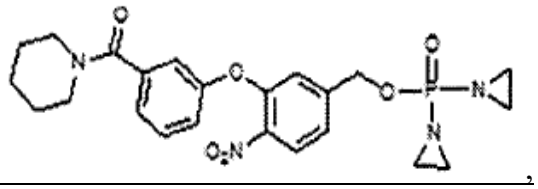
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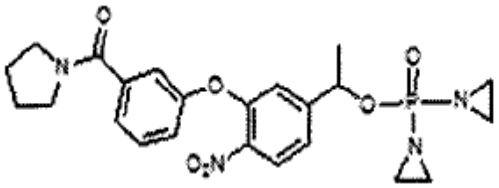
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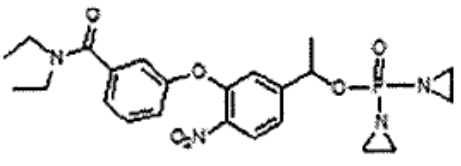
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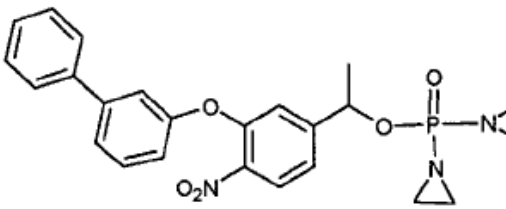
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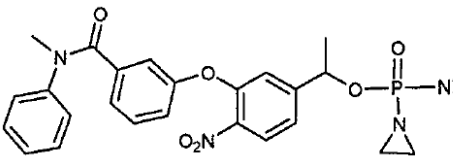
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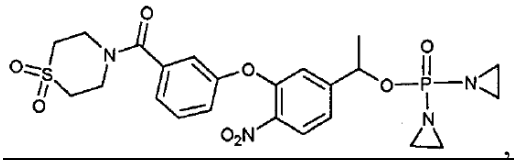
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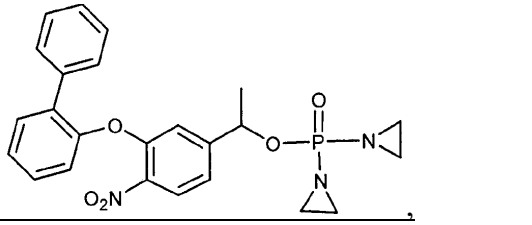
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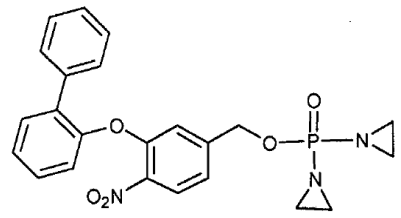
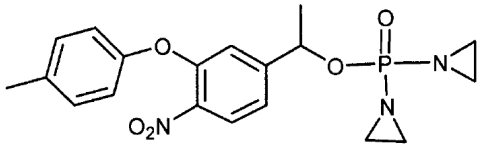
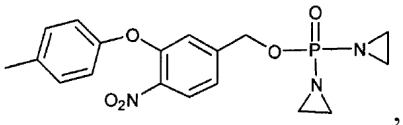
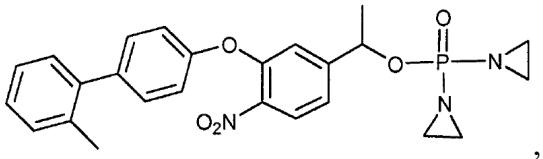
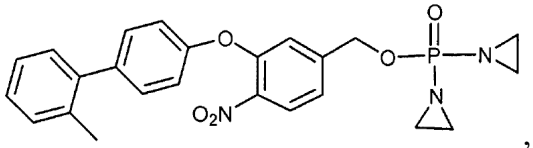
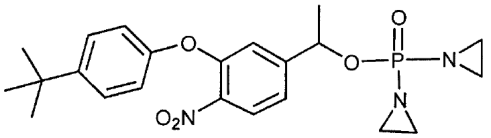
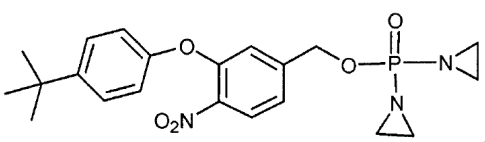
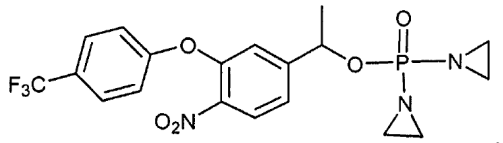
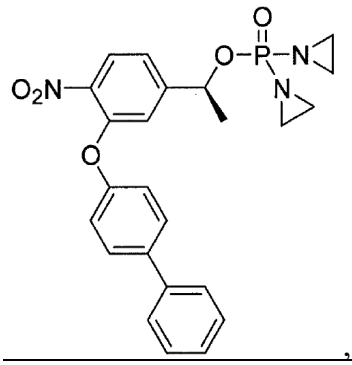
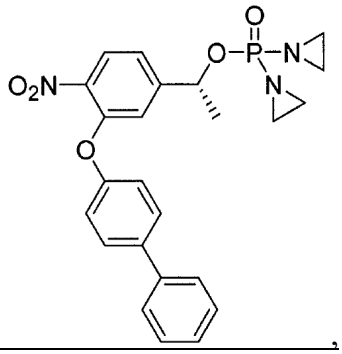
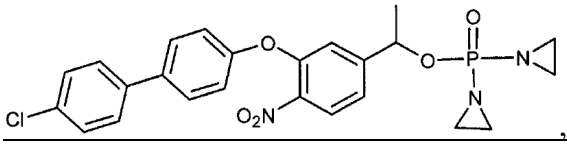
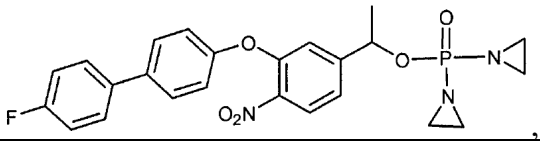
 ,  ,

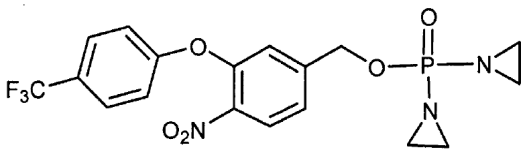
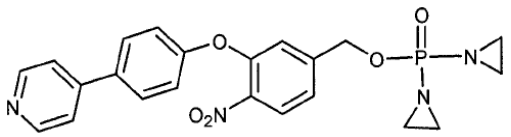
 ,  ,

 ,  ,

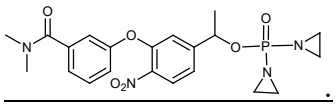
 ,  ,

 ,  ,

 ,  ,

 and  .

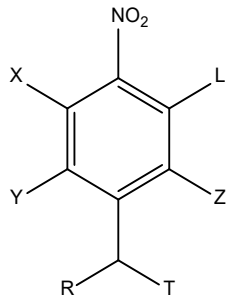
19. The compound of claim 1, wherein the compound is



13.20. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-1219and at least a pharmaceutically acceptable excipient or carrier.

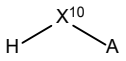
14.21. The pharmaceutically acceptable composition of claim 20 for treating Use of the compound of any one of claims 1-12 or the composition of claim 13 in the manufacture of a medicament for the treatment of cancer in a patient.

15.22. 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.

16.23. The pharmaceutically acceptable Use of the compound of any one of claims 1-12 or the composition of claim 2013 in the manufacture of a medicament for the treatment of cancer in a patient, wherein a an AKR1C3 protein expression level of a cancer in a patient using an AKR1C3 antibody is detectablereductase level of the cancer is equal to or greater than a predetermined value.

~~17.~~24. The pharmaceutically acceptable composition~~Use~~ of claim ~~16~~20, wherein ~~the AKR1C3 reductase level of the cancer is~~ an intratumoral AKR1C3 protein expression~~reductase~~ level of ~~the~~ a cancer in a sample isolated from ~~the~~ a patient using an AKR1C3 antibody is detectable.

~~18.~~25. A kit comprising a means for isolating a sample from a patient and determining an intratumoral AKR1C3 protein expression~~reductase~~ level of ~~the~~ a cancer in the sample using an AKR1C3 antibody; and a means for indicating ~~determining~~ whether the intratumoral AKR1C3 protein expression level of the cancer is equal to or greater than a predetermined level at which a compound of any one of claims 1-~~12~~ 19 or a composition of any one of claims 20-21 and 23-24~~claim 13~~ should be administered.