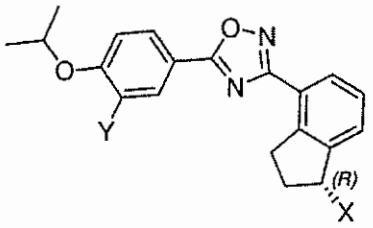
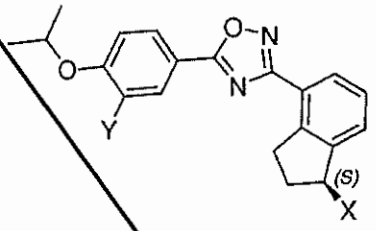
We claim:

1. A compound having the structure of Formula **I-R** or **I-S** or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof:



I-R



I-S

wherein

X is –NR′R″ or -OR‴;

Y is –CN, -Cl, -CF_3, I, -COOH, or -$COOR^1$;

R′ is H, C_{1-4} alkyl, n-hydroxy C_{1-4} alkyl, -SO_2-R^1, or -CO-R^1;

R″ is H, -SO_2-R^3 , C_{1-4} alkyl optionally substituted with 1 or more R^2, or a ring moiety optionally substituted with R^4 wherein such ring moiety is piperidinyl, cyclohexyl, morpholinyl, thiazolyl, pyrazolyl, pyrrolidinyl, imidazolyl, or phenyl;

R‴ is H, C_{1-4} alkyl, or -CO-R^1

or R′ and R″ taken together with the nitrogen atom to which they are bound form a 4, 5, or 6 membered saturated heterocyclic ring containing 0 or 1 additional heteroatoms where such additional heteroatom is O or N wherein such heterocycle is optionally singly or multiply substituted with substituents independently selected from the group consisting of –OH, oxo, -NH_2, n-hydroxy-C_{1-4} alkyl, -COOH, -$(CH_2)_m$-COOH, -$(CH_2)_m$-$COOR^1$, -$N(R^1R^1)$, and -$(CH_2)_m$-CO-$N(R^5R^5)$;

each R^1 is independently C_{1-4} alkyl or H;

each R^2 is independently H, halo, OH, oxo, =NH, NH_2, -COOH, F, -NHR^1, -$N(R^5R^5)$,–SO_2-R^1, –SO_2-$N(R^5R^5)$, -$N(R^1)$–SO_2-R^1, -$COOR^1$, -OCO-R^1, -CO-$N(R^5R^5)$, -$N(R^1)$-COR^1, C_{1-3} alkyl, C_{1-3} alkoxy, and a ring moiety optionally substituted with R^4 wherein such ring moiety is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, pyrazolyl, imidazolyl, benzimidazolyl, azetidinyl, cyclobutinyl, or phenyl;

each R^3 is independently R^2, C_{1-4} alkyl, C_{3-6} cycloalkyl, or C_{1-4} alkyl optionally substituted with 1 or more R^2;

each R^4 is independently halo, OH, $-NH_2$, $-NHR^1$, $-N(R^1R^1)$, -COOH, $-COOR^1$, $-NHCO-R^1$;

each R^5 is independently C_{1-4} alkyl or H, or two R^5 taken together with the nitrogen atom to which they are bound form a 4, 5, or 6 membered saturated heterocyclic ring containing 0 or 1 additional heteroatoms where such additional heteroatom is O or N wherein such heterocycle is optionally substituted with –OH, $-NH_2$, $-N(R^1R^1)$, n-hydroxy C_{1-4} alkyl, $-(CH_2)_m-COOH$, $-(CH_2)_m-COOR^1$;

each m is independently 0, 1, 2, or 3.

2. The compound of claim 1 wherein the compound has the structure of Formula **I-R** or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

3. The compound of claim 1 wherein the compound has the structure of Formula **I-S** or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

4. The compound of claims 1-3 wherein the compound is substantially enantiomerically pure.

5. The compound of claim 4 wherein the compound has an EC_{50} as an S1P receptor subtype 1 agonist which is at least ten times smaller than its EC_{50} as an agonist of a mutant S1P receptor subtype 1 having a single mutation with respect to wild type S1P receptor subtype 1 such that the 101st amino acid residue is changed from asparagine to alanine.

6. The compound of claim 5 wherein the compound has an EC_{50} as an S1P receptor subtype 1 agonist which is at least twenty times smaller than its EC_{50} as an agonist of a mutant form of S1P receptor subtype 1 having a single mutation with respect to wild type S1P receptor subtype 1 such that the 101st amino acid residue is changed from asparagine to alanine.

7. The compound of claims 1-6 wherein the compound has a therapeutic index of at least 5 as measured in rats following 5 or 14 days of dosing with the compound where the therapeutic index is the ratio of the dose achieving less than or equal to 10% increase in lung to terminal body weight at the conclusion of such 5 or 14 days and the dose achieving 50% lymphopenia.

8. The compound of claim 7 wherein the therapeutic index is at least 10.

9 The compound of claim 7 wherein the therapeutic index is at least 20.

10. The compound of claims 7-9 wherein the therapeutic index for the compound is greater than the therapeutic index for the enantiomer of the compound.

11. The compound of claim 10 wherein the therapeutic index for the compound is at least 150% of the therapeutic index for the enantiomer of the compound.

12. The compound of claims 1-11 wherein Y is Cl.

13. The compound of claims 1-11 wherein Y is CF_3.

14. The compound of claims 1-11 wherein Y is CN.

15. The compound of claims 1-14 wherein X is –NR′R″.

16. The compound of claims 1-14 wherein X is –OR‴.

17. The compound of claim 16 wherein X is –OH.

18. The compound of claim 16 wherein X is –OCO-R^1.

19. The compound of claim 18 wherein R^1 is C_{1-3} alkyl.

20. The compound of claim 15 wherein R′ is H.

21. The compound of claim 15 wherein R′ is -COR^1.

22. The compound of claim 15 wherein R′ is -SO_2-R^1.

23. The compound of claim 15 wherein R″ is H.

24. The compound of claim 15 wherein R″ is -SO_2-R^3.

25. The compound of claim 15 wherein R″ is C_{1-4} alkyl optionally substituted with 1 or more R^2.

26. The compound of claim 15 wherein R″ is –$(CR^aR^b)_n$-R^2 ; each R^a and each R^b is independently selected from the group consisting of H, hydroxyl and methyl or R^a and R^b bound to the same carbon taken together are oxo; and n is 0, 1, 2, or 3.

27. The compound of claim 26 wherein n is 2.

28. The compound of claim 27 wherein R^2 is –OH, -NH_2, -NHR^1, -$N(R^5R^5)$, or –COOH.

29. The compound of claim 24 wherein R^3 is C_{1-4} alkyl optionally substituted with 1 or more R^2.

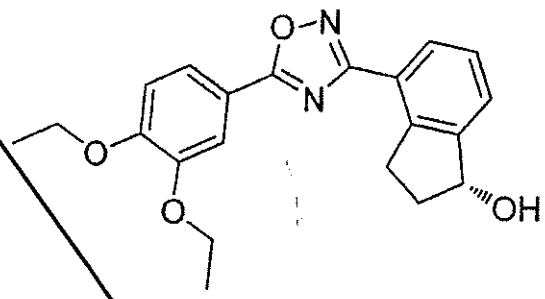
30. The compound of claim 24 wherein Y is CN.

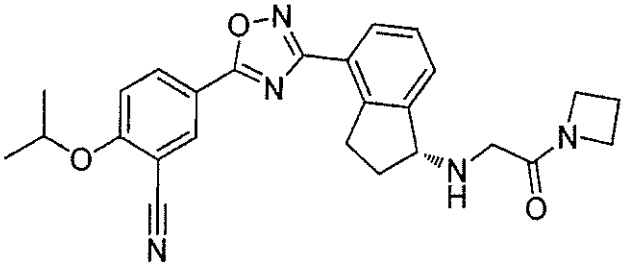
31. The compound of claim 29 wherein R^3 is –C_2H_5-N((R^5R^5) or –CH_2-CO-N(R^5R^5).

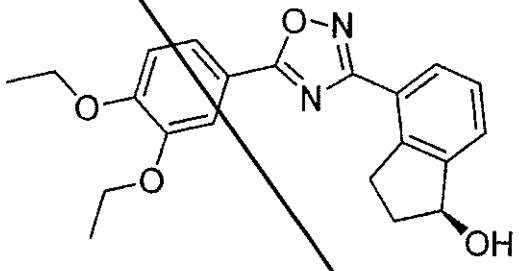
32. The compound of claim 30 wherein R^3 is C_2H_5–O-R^1.

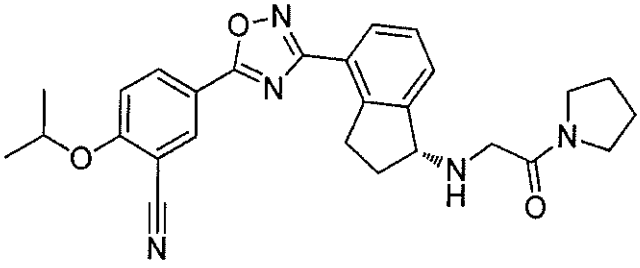
33. The compound of claim 14 wherein X is –NH-CO-N(R^5R^5).

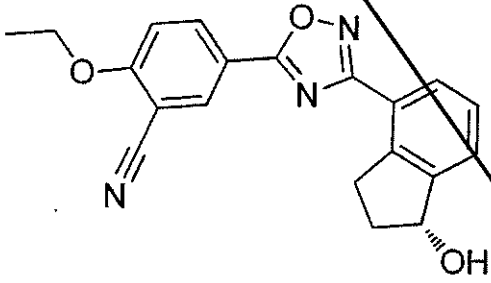
34. The compound of claim 1 wherein the compound is selected from **compounds 1-253**:

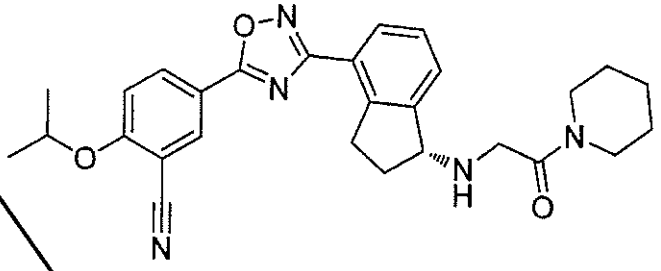


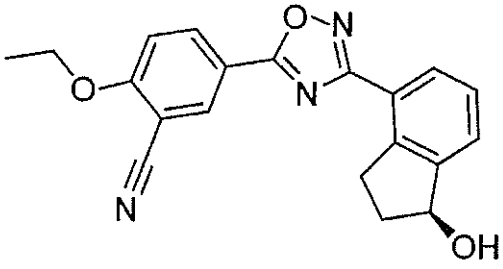


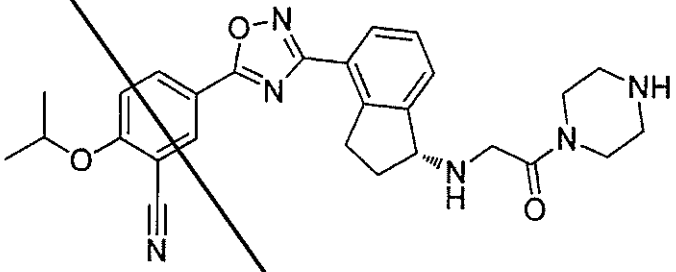


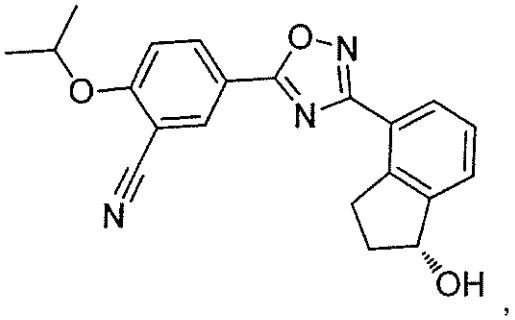


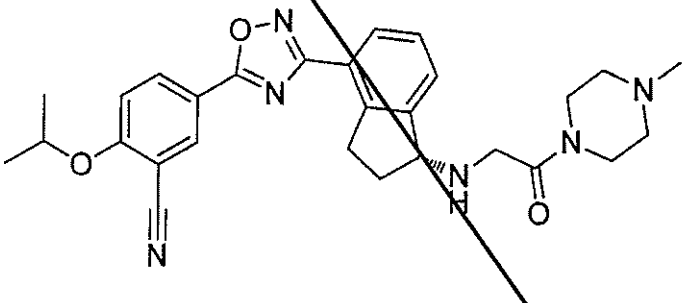


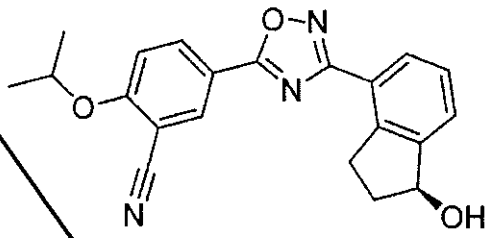












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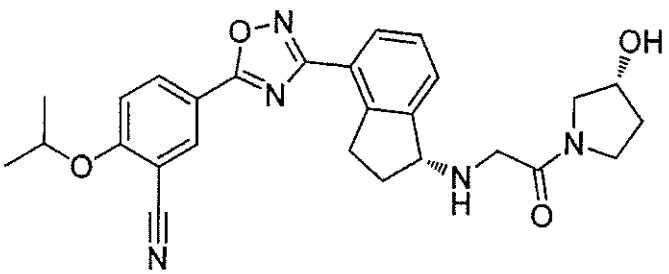

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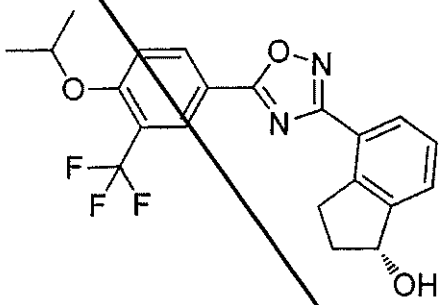

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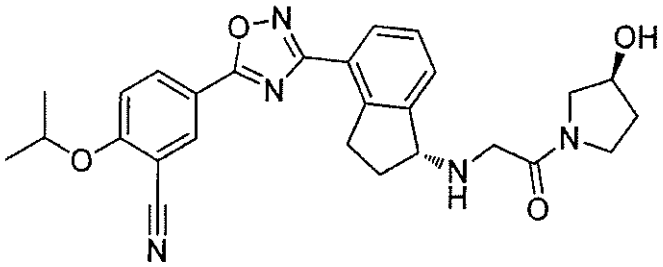

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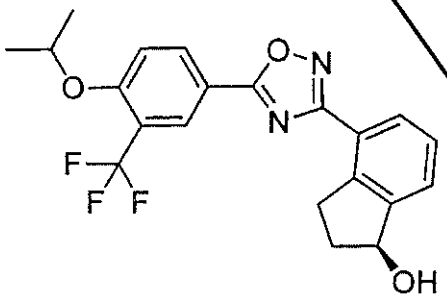

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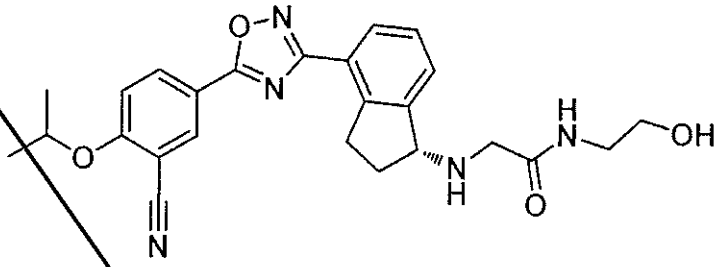

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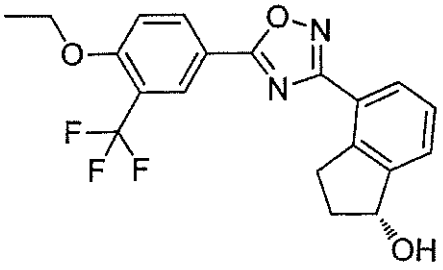

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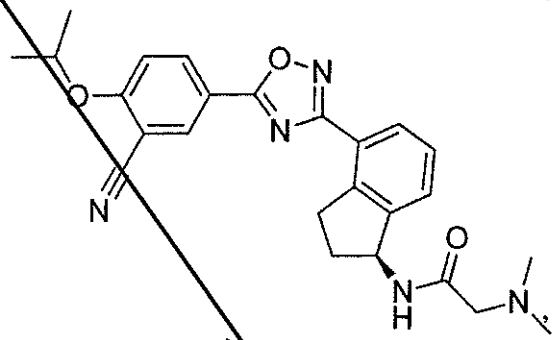

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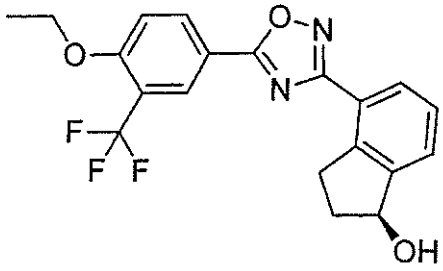

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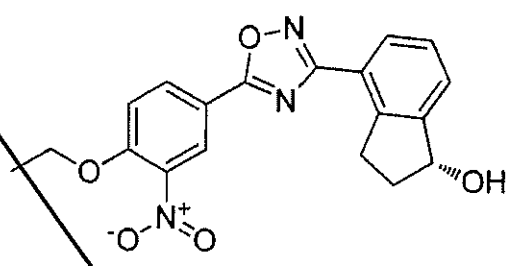

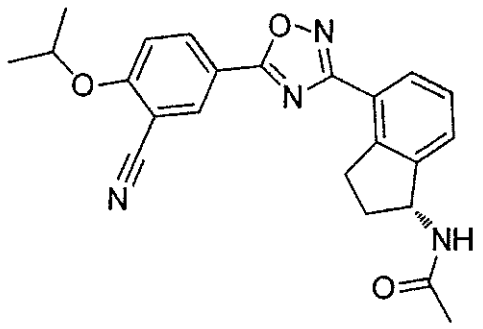

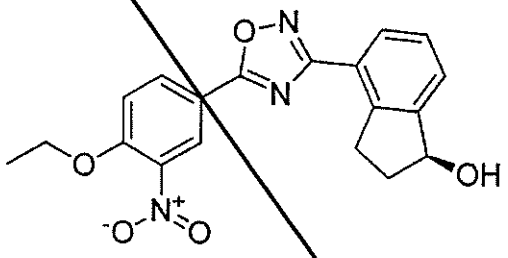

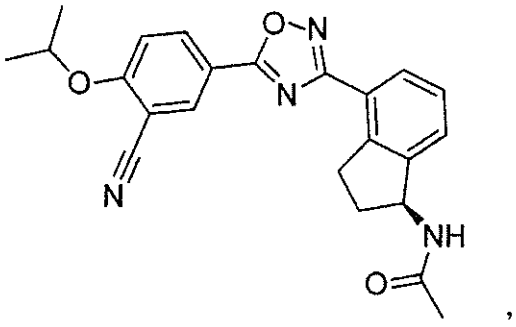

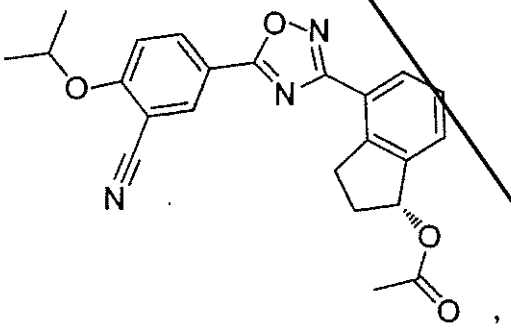

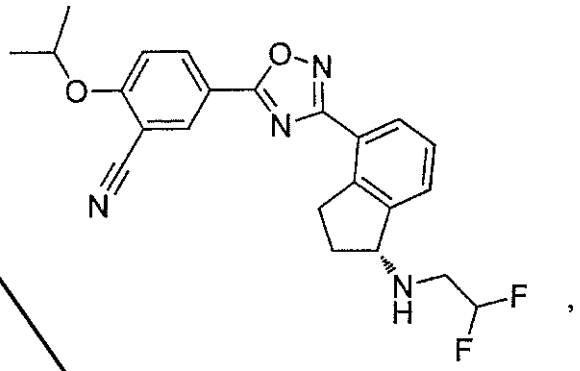

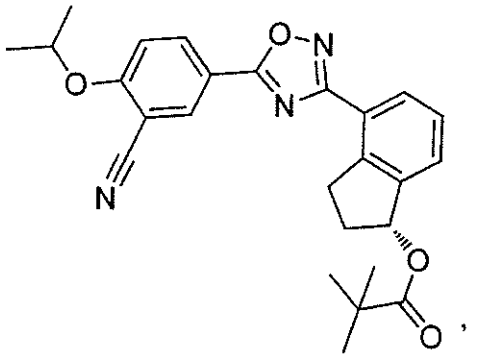

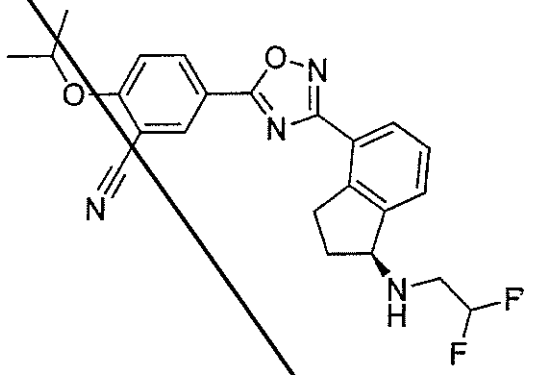

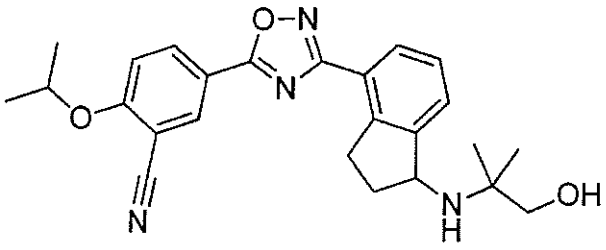

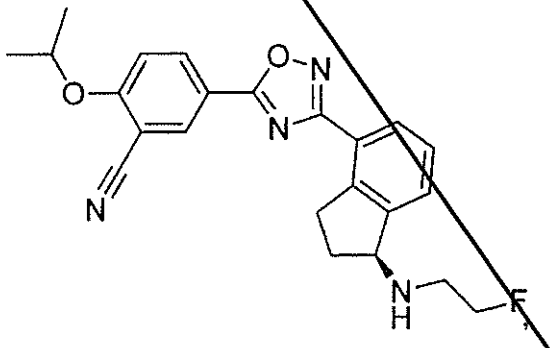

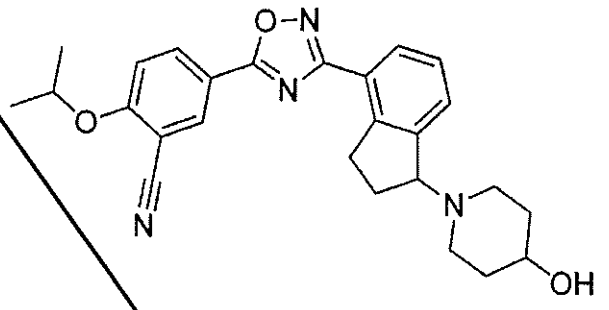

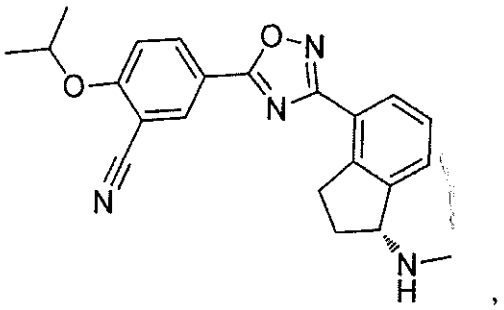

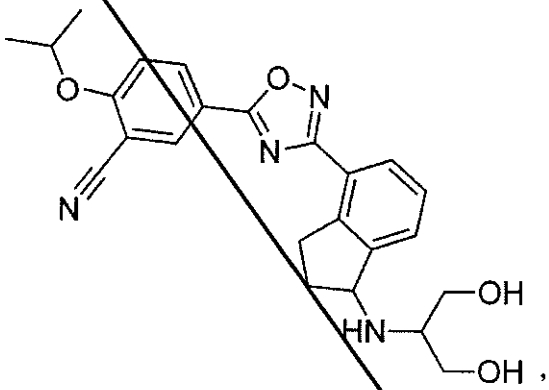

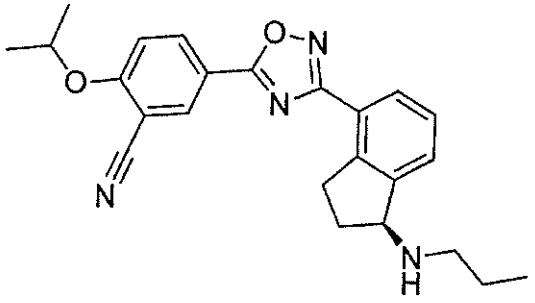

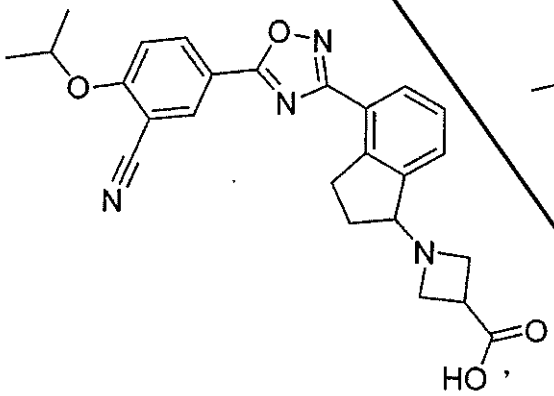

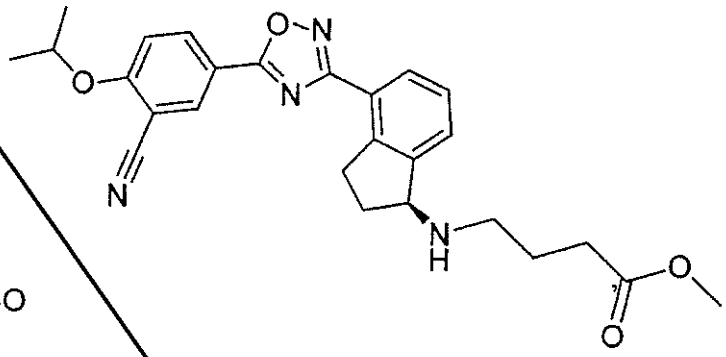

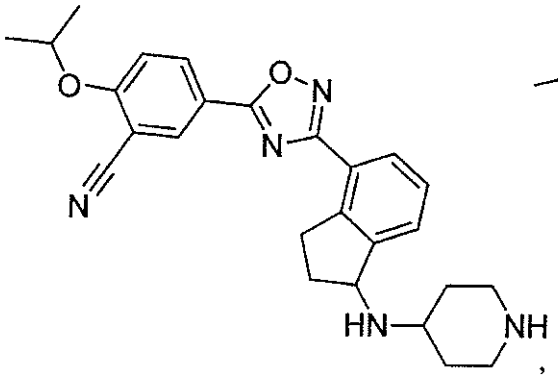

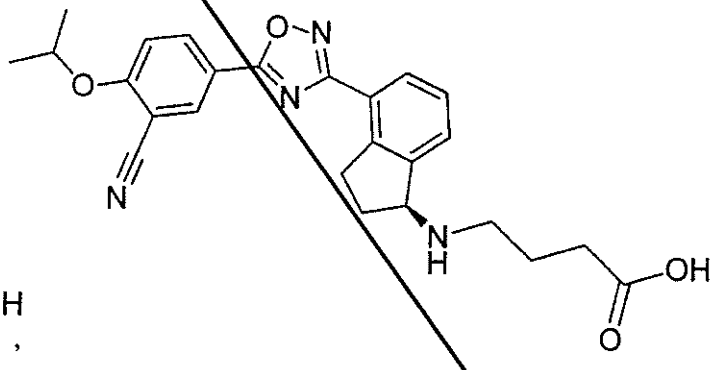

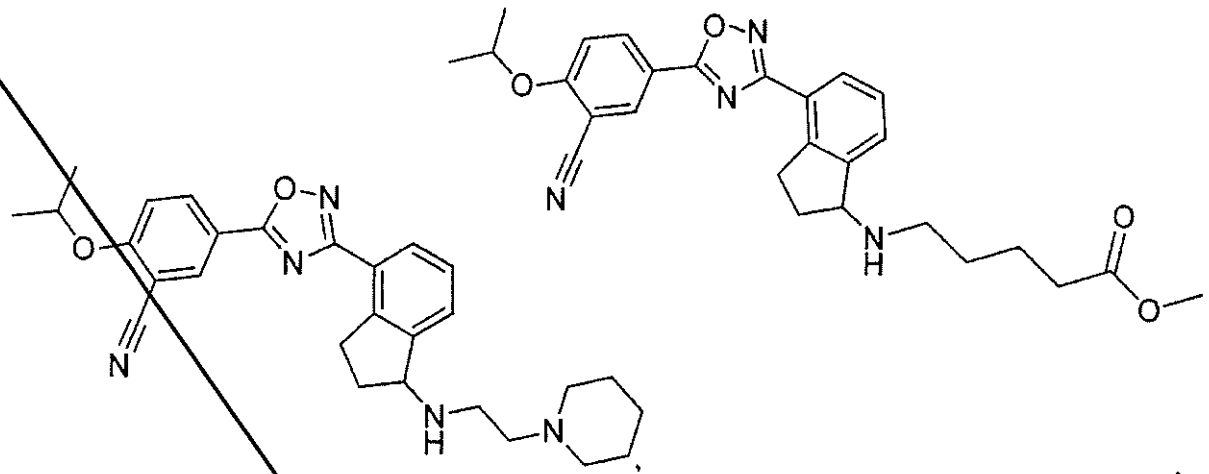

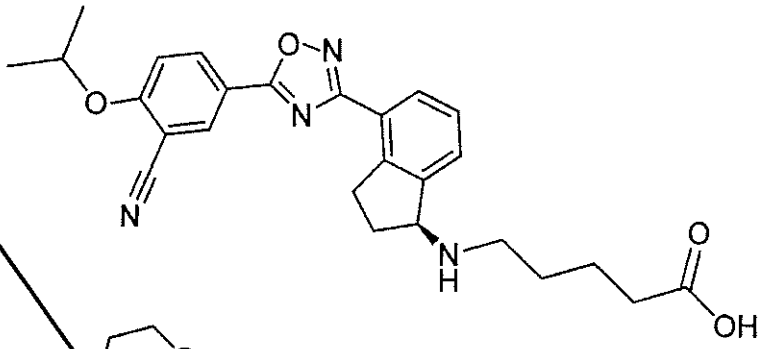

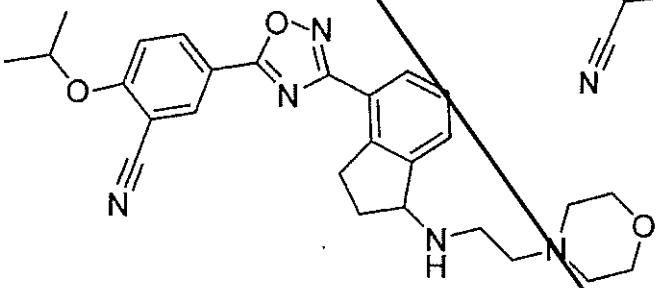

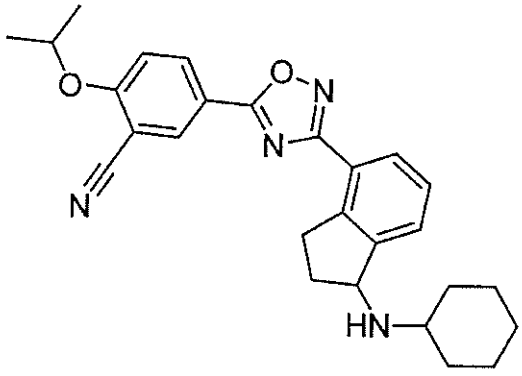

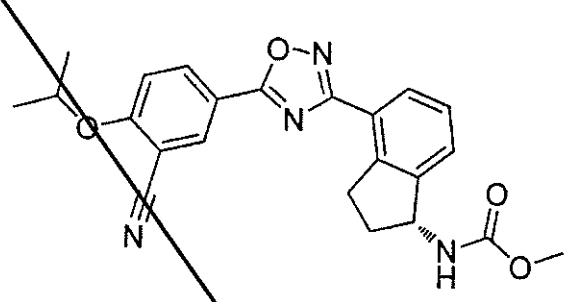

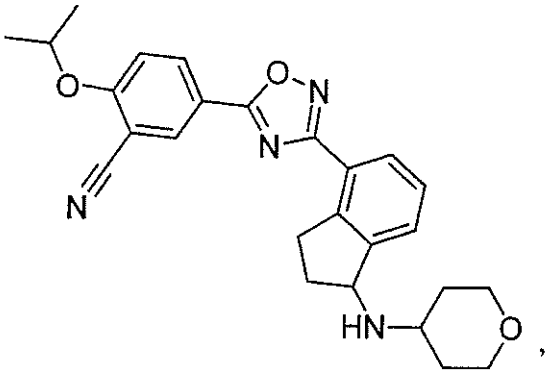

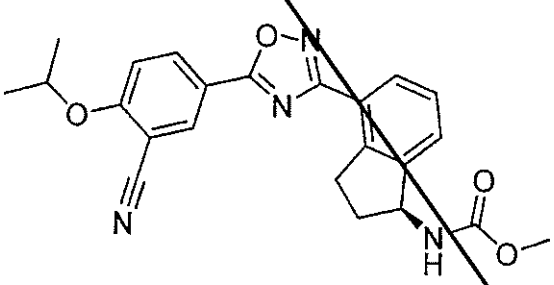

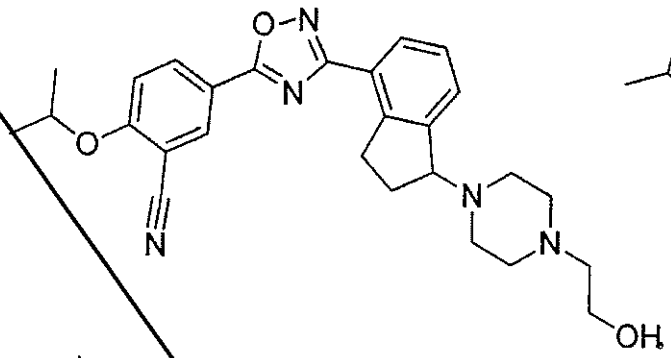

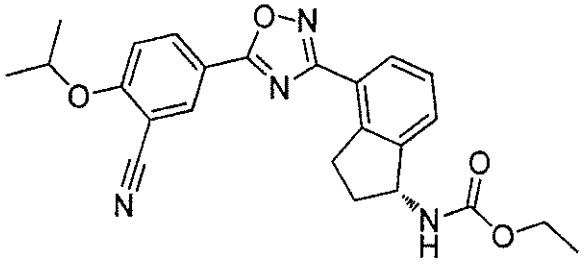

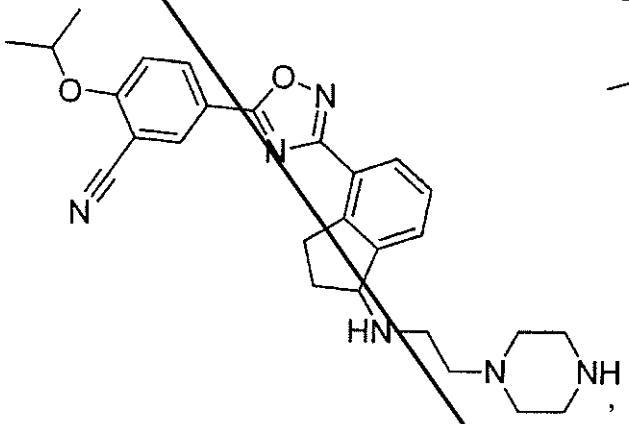

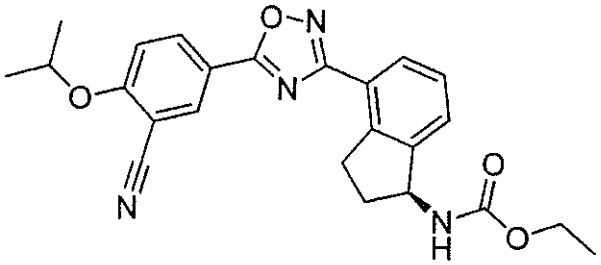

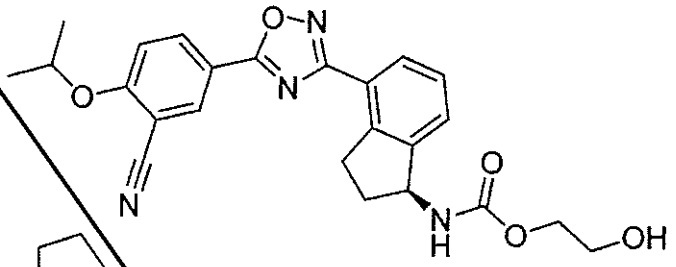

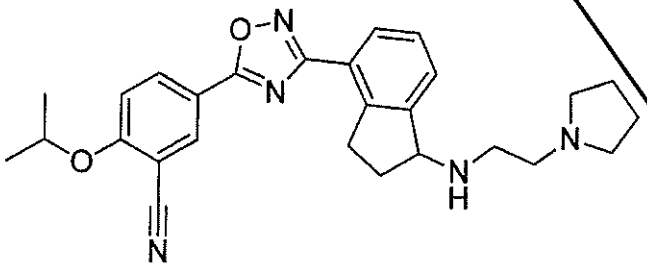

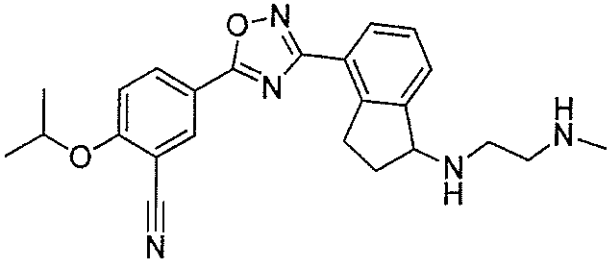

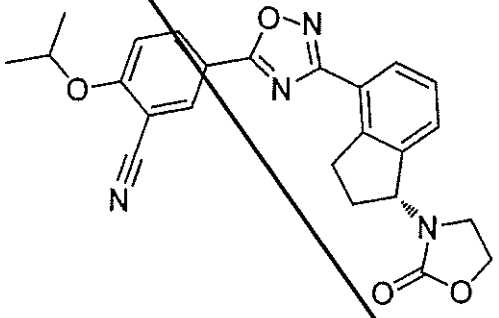

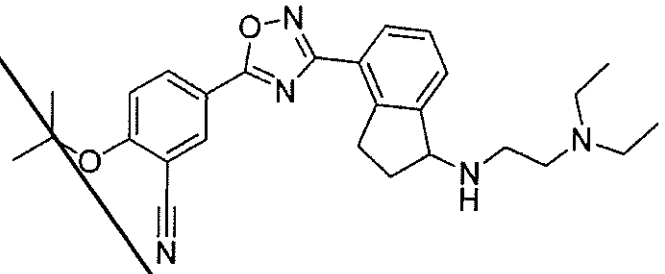

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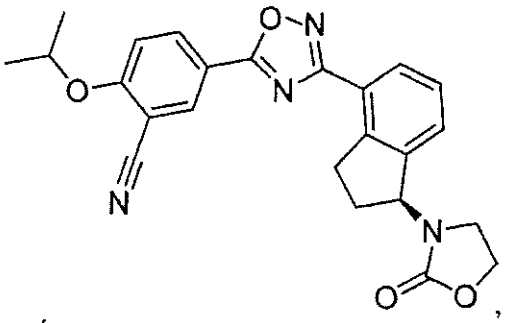

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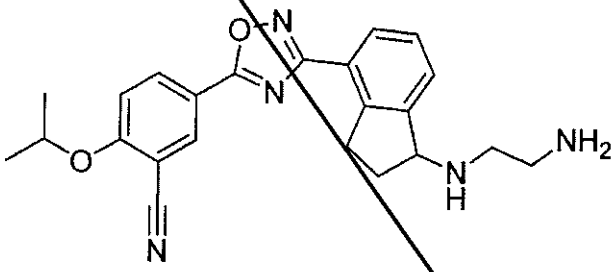

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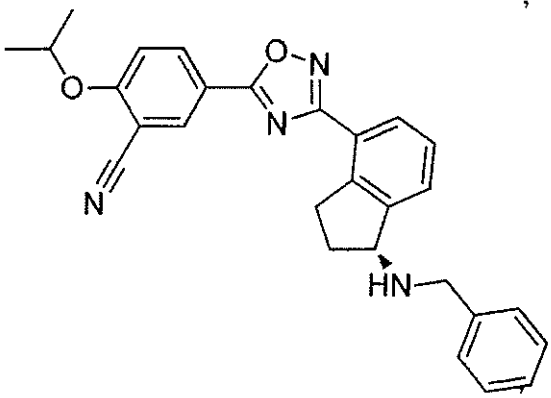

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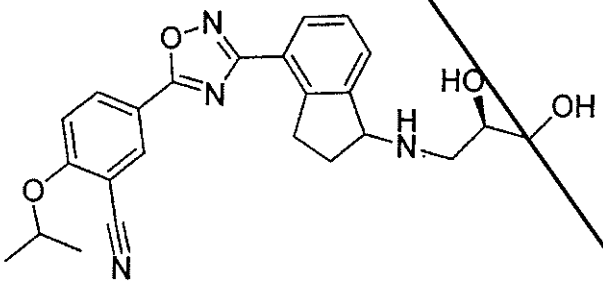

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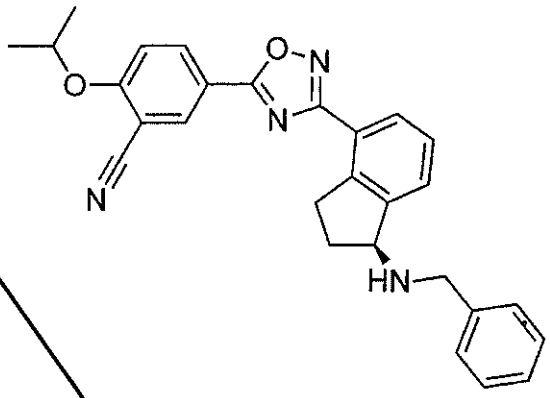

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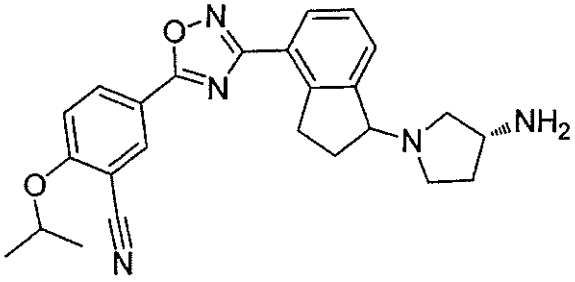

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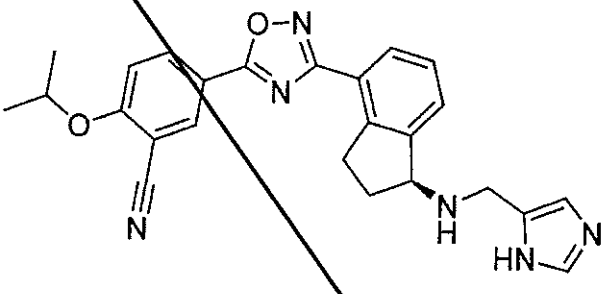

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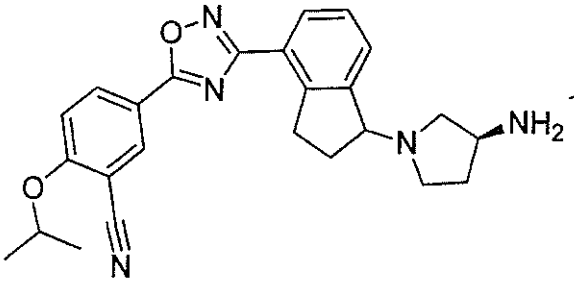

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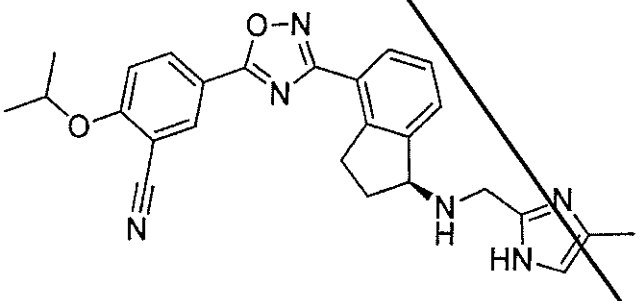

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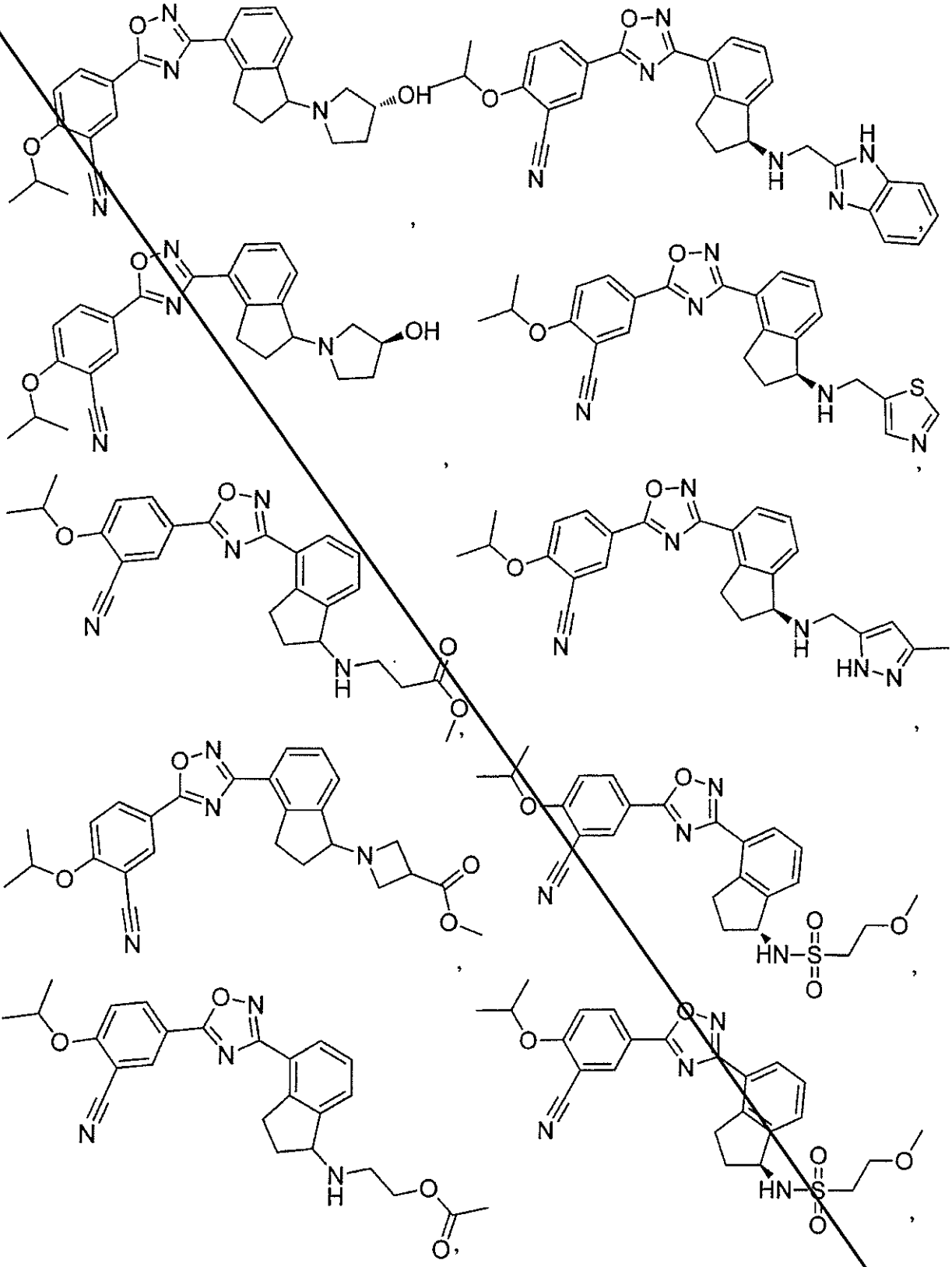

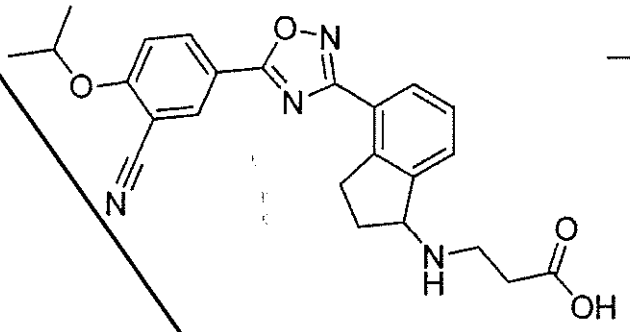

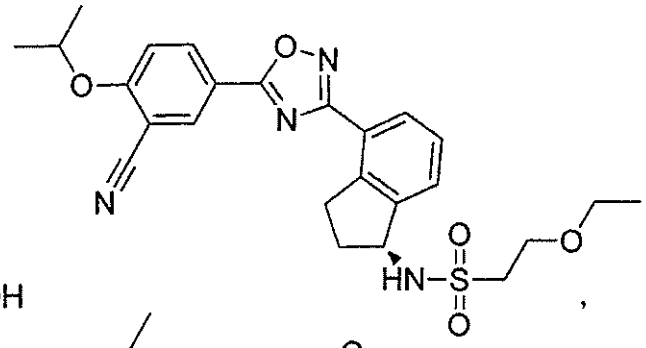

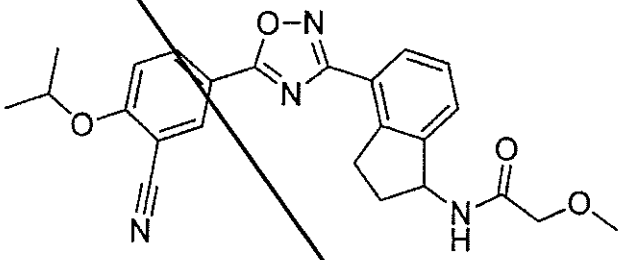

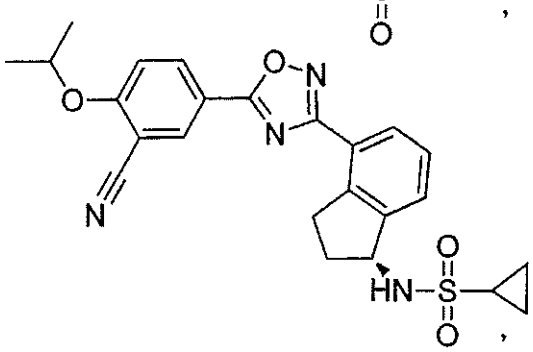

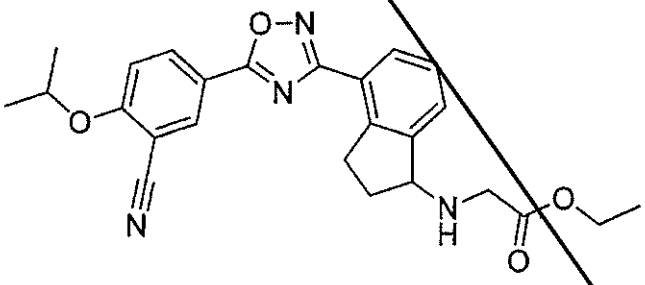

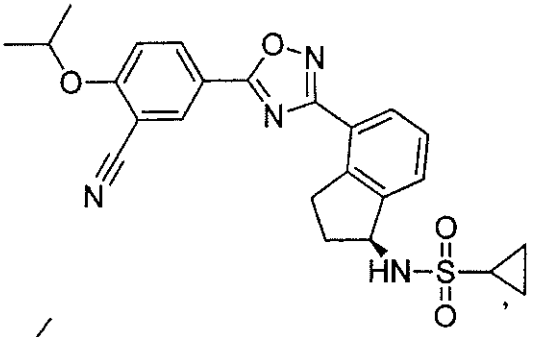

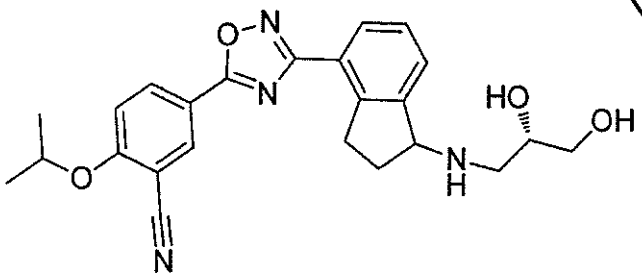

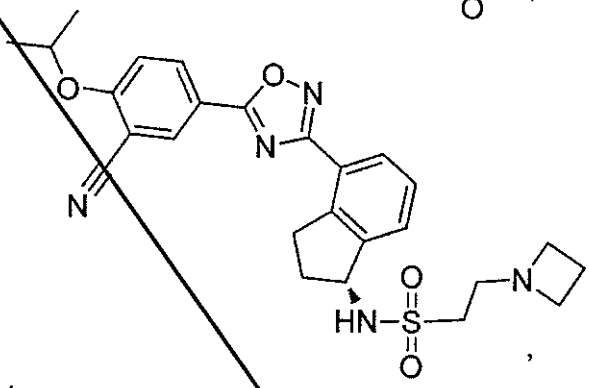

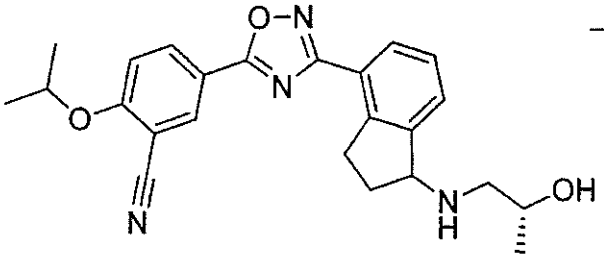

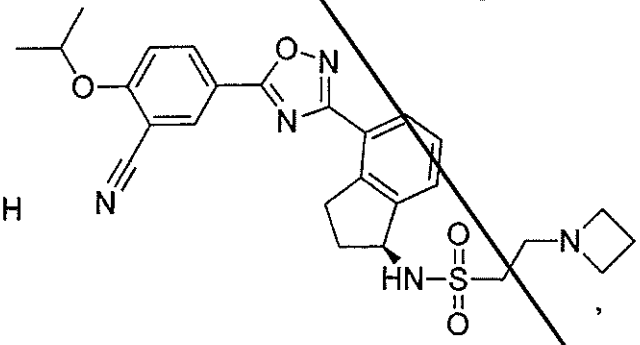

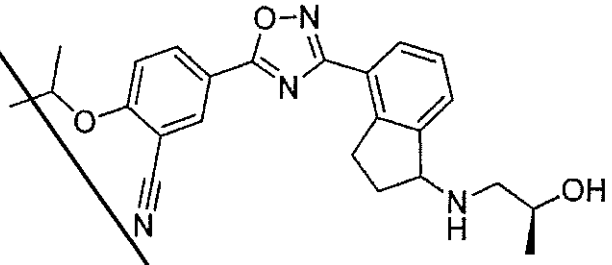

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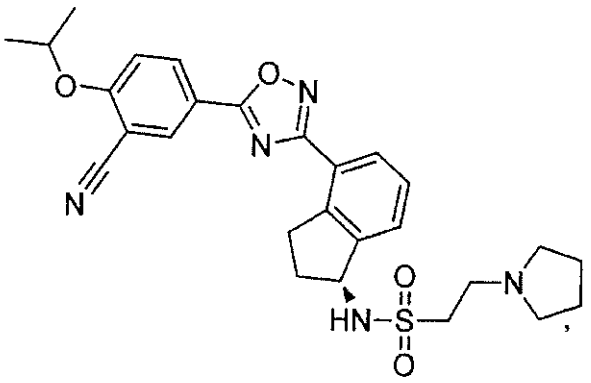

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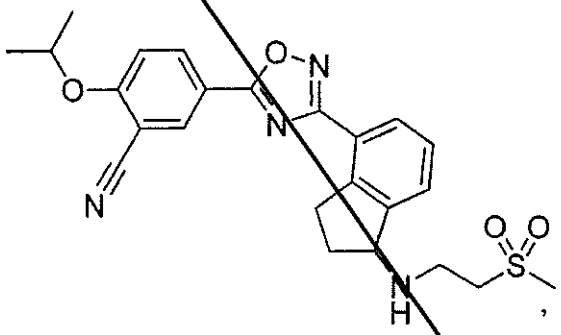

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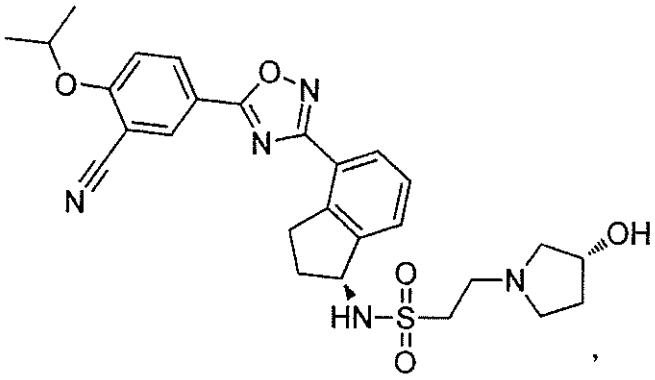

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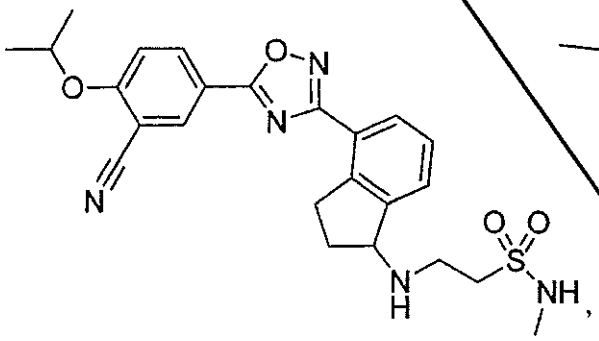

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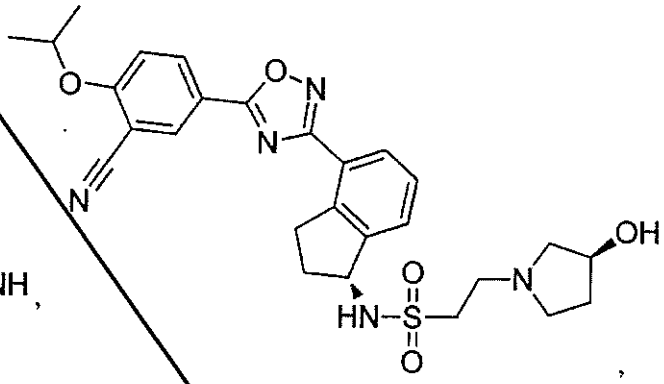

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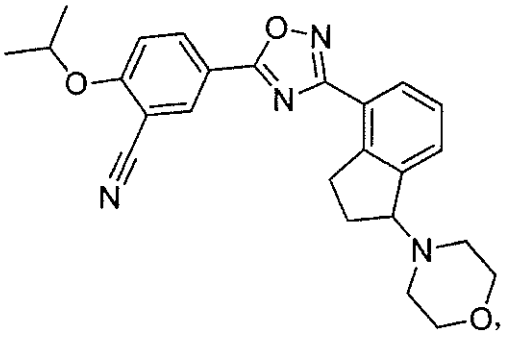

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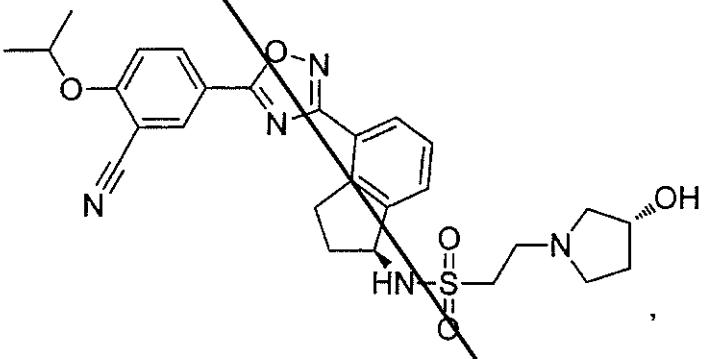

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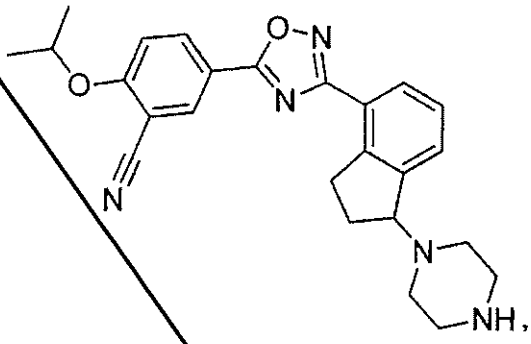

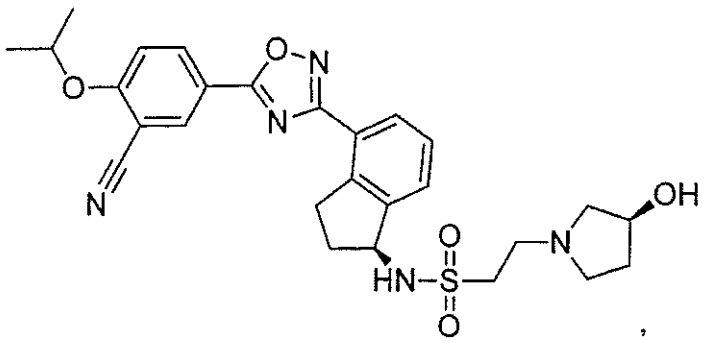

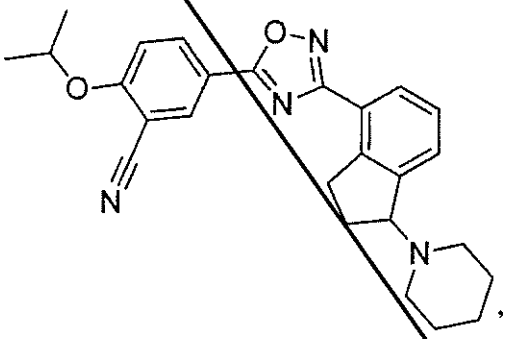

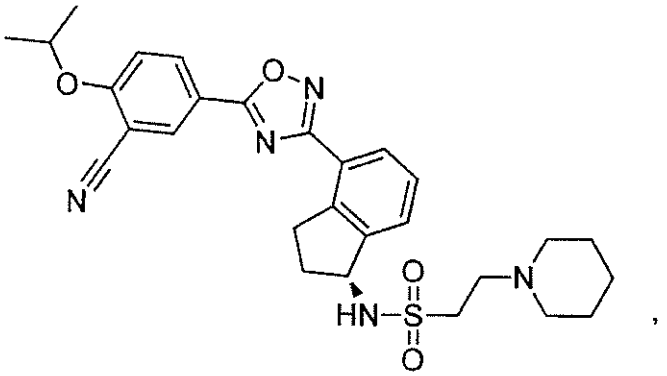

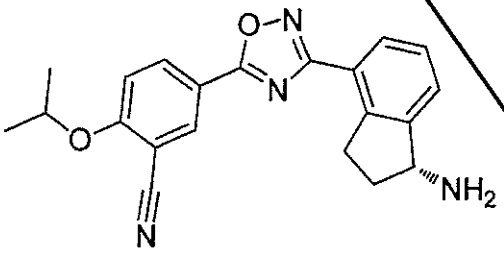

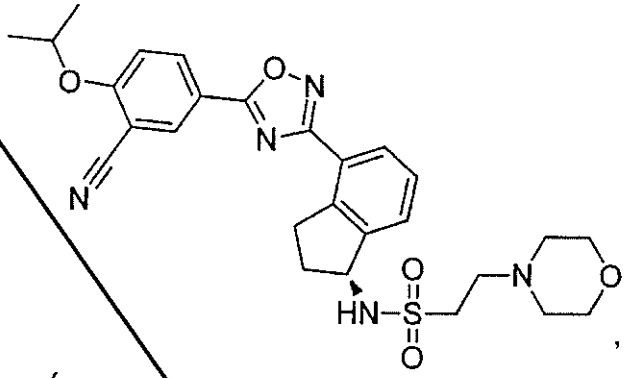

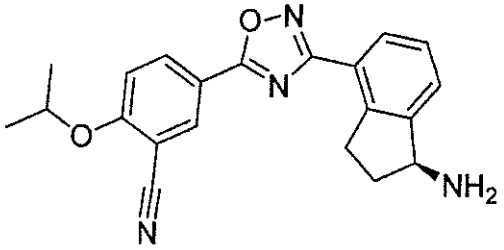

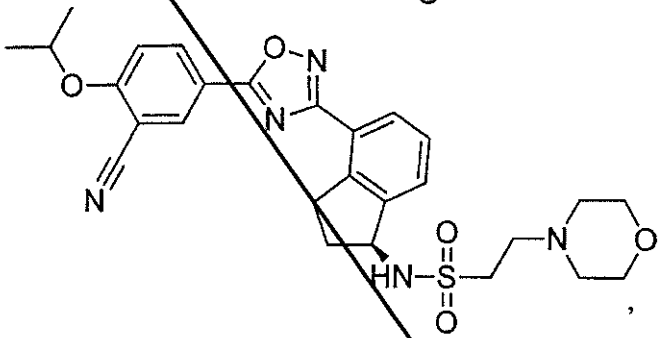

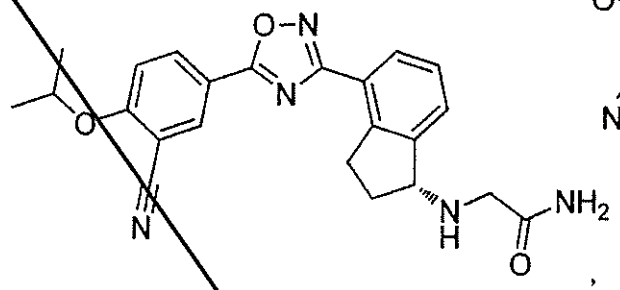

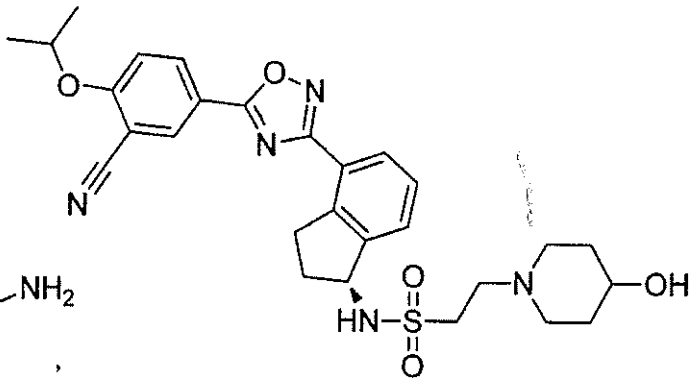

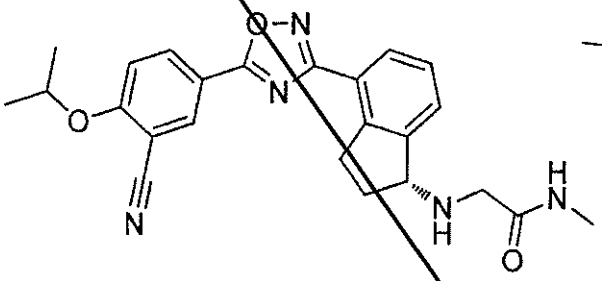

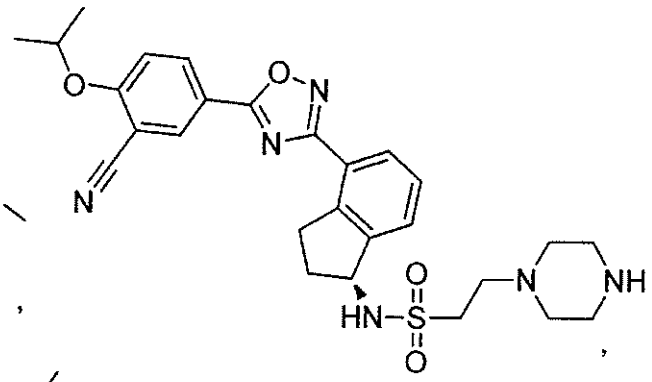

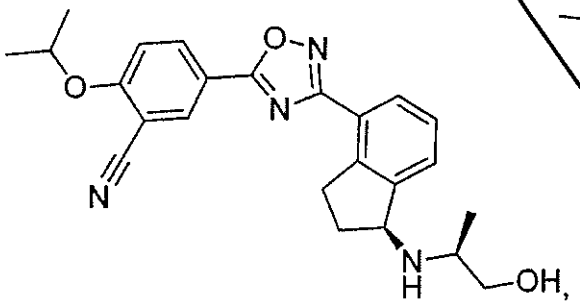

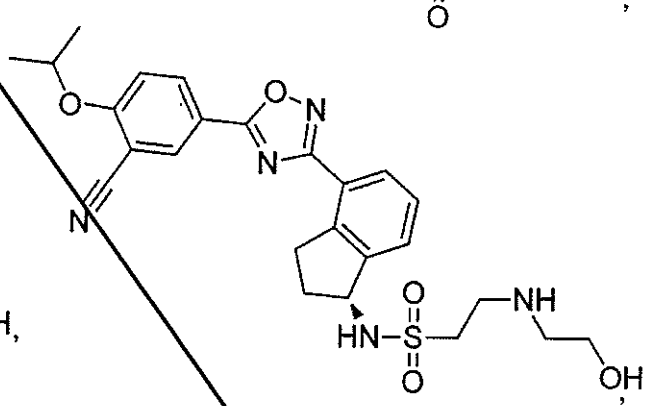

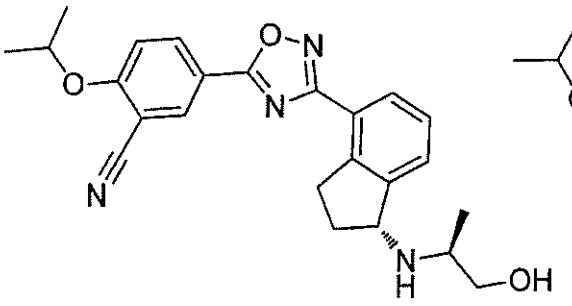

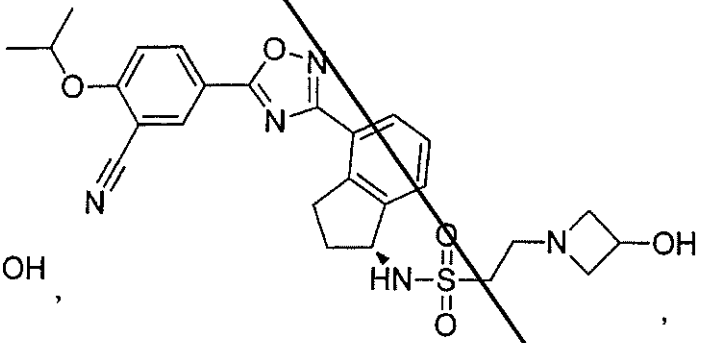

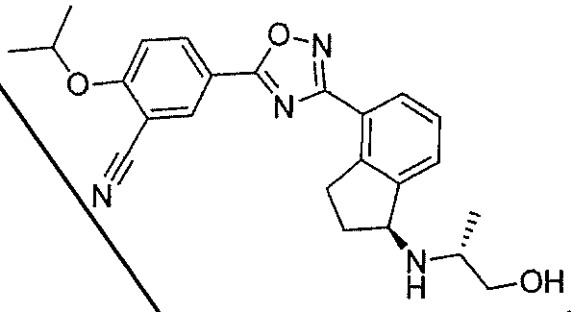

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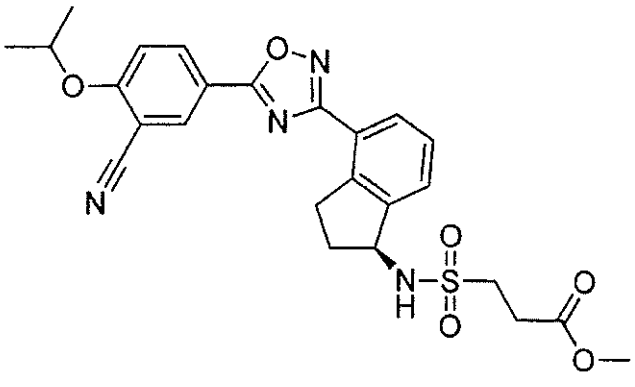

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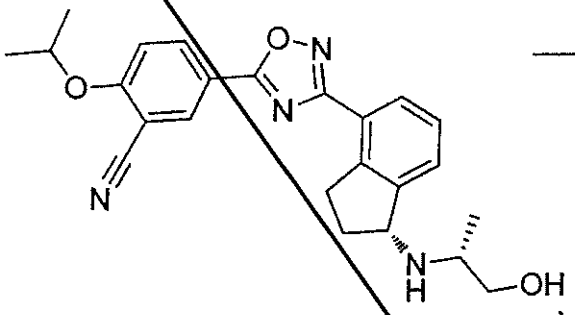

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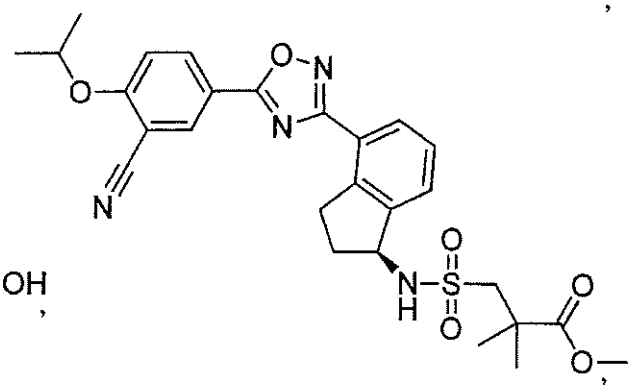

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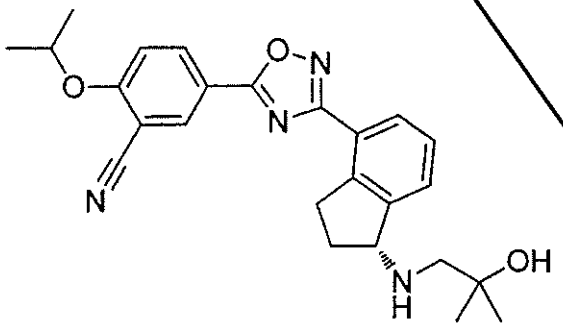

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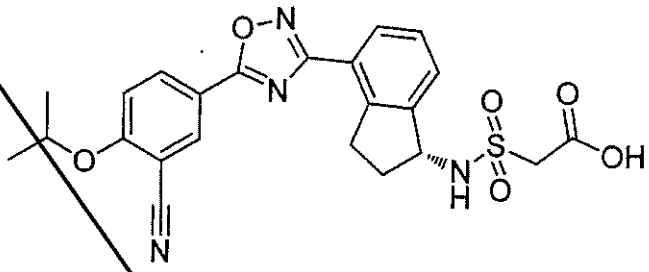

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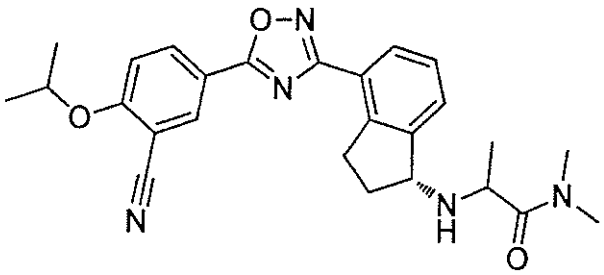

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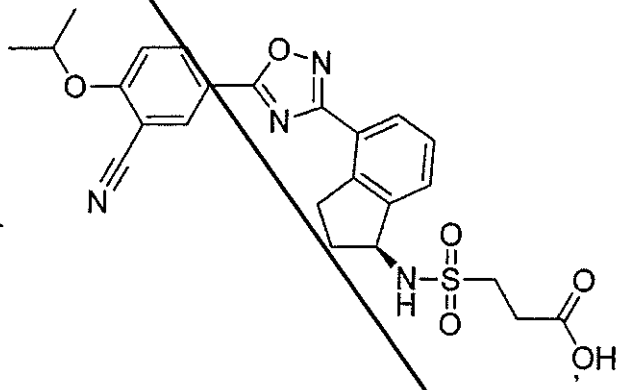

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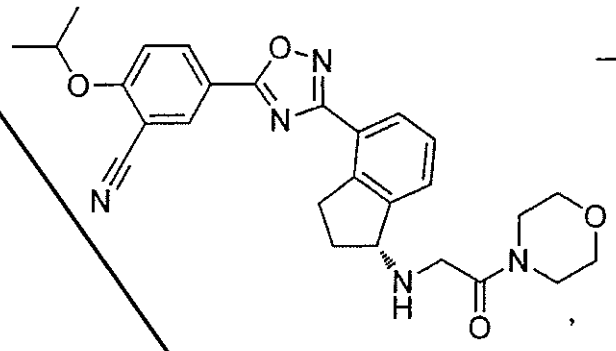

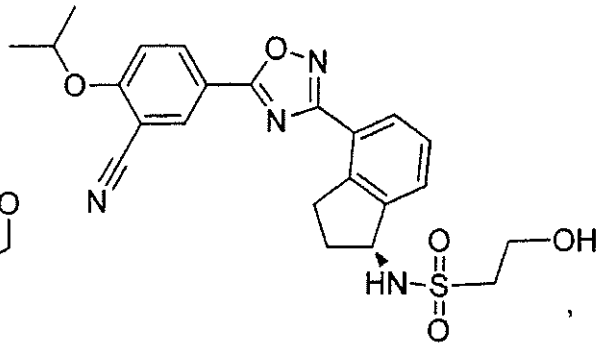

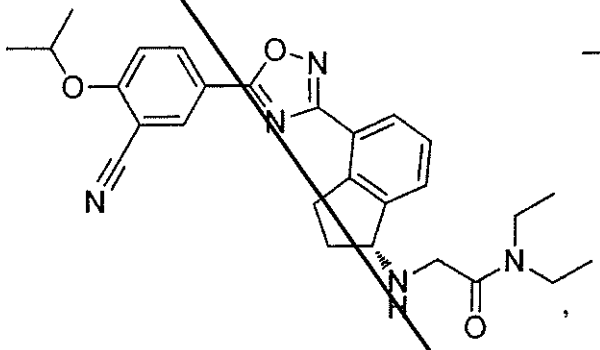

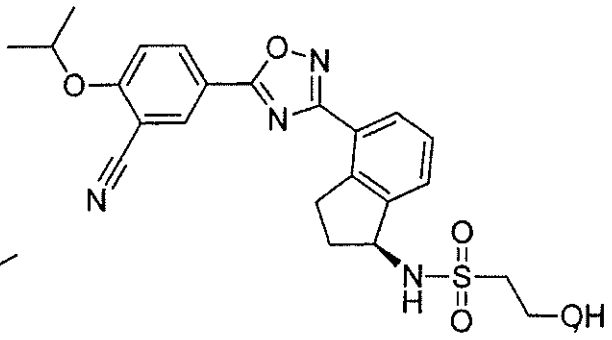

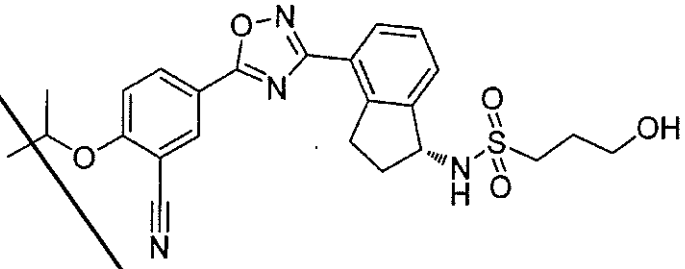

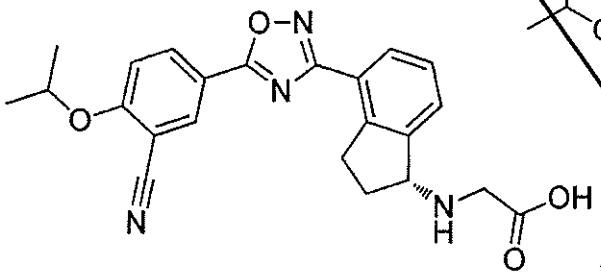

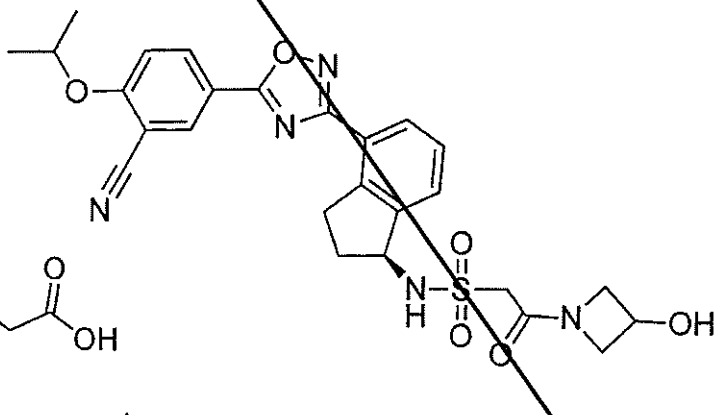

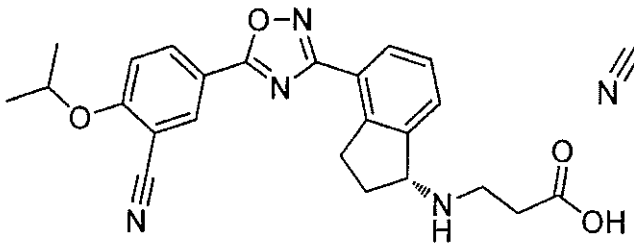

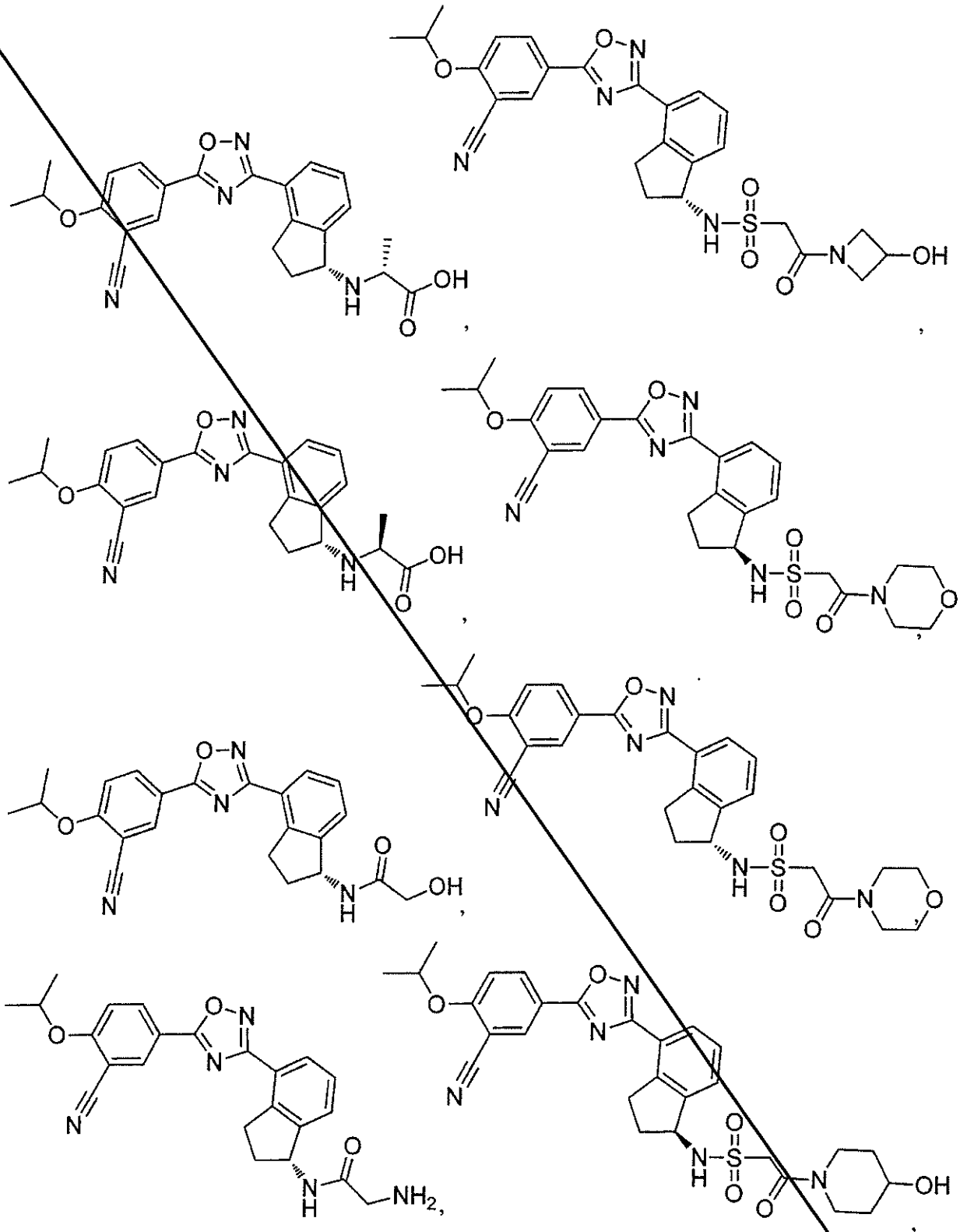

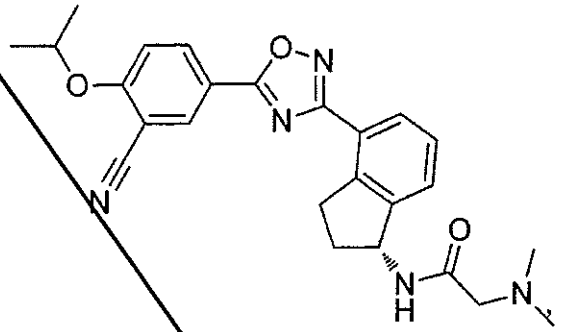

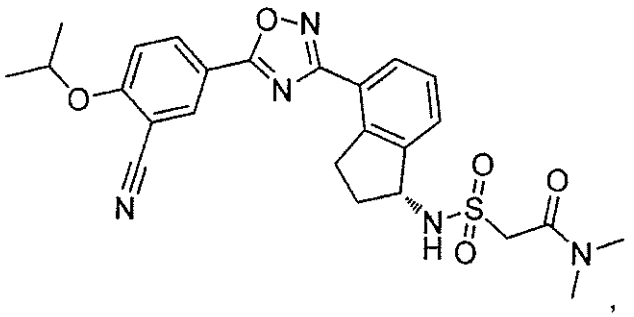

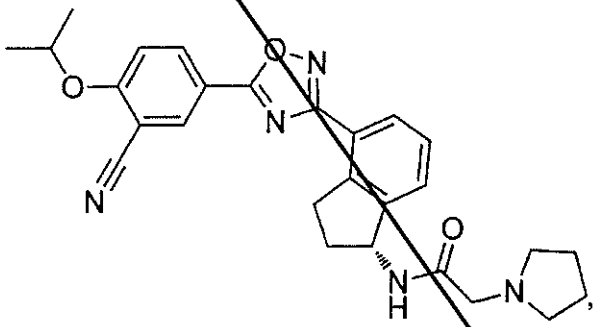

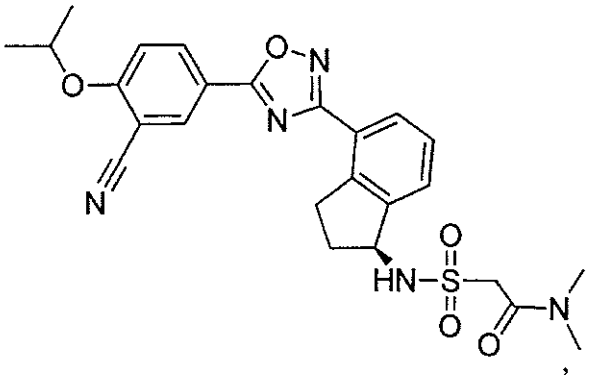

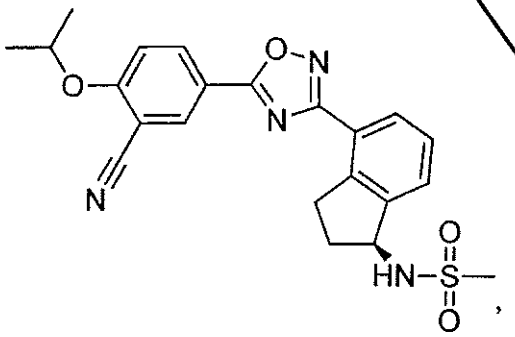

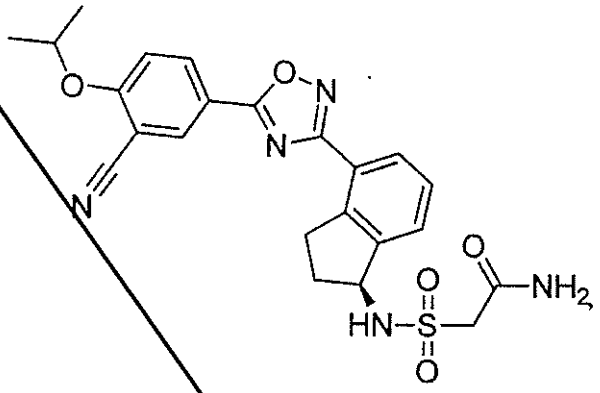

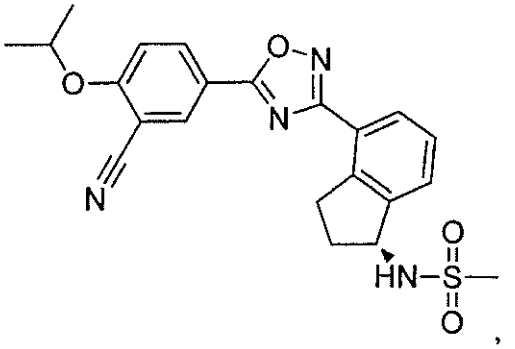

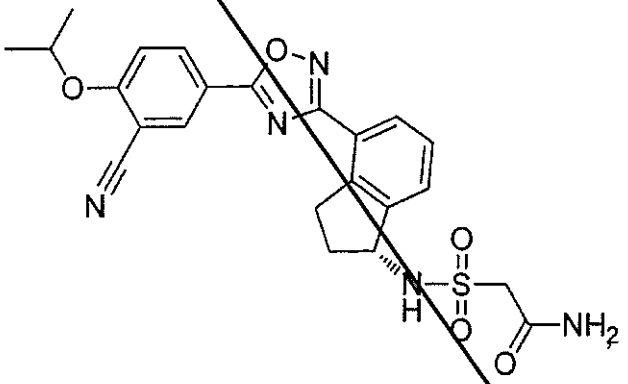

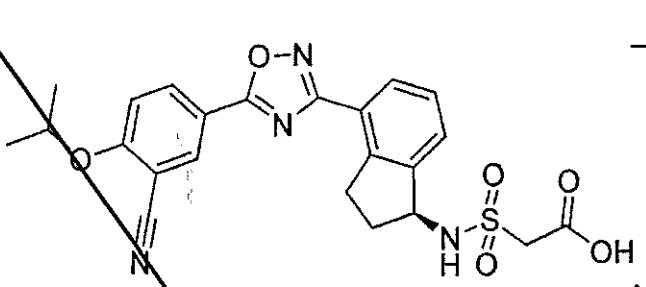

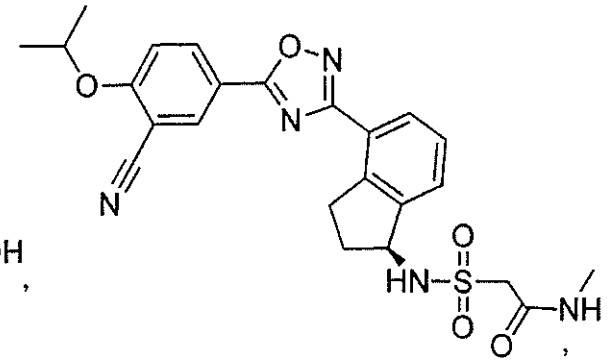

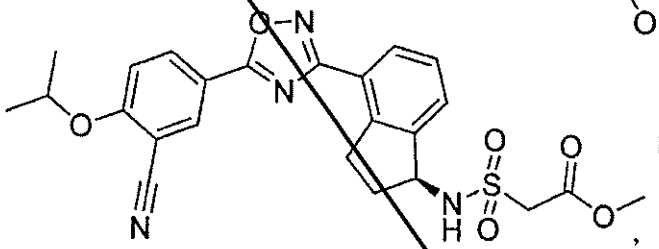

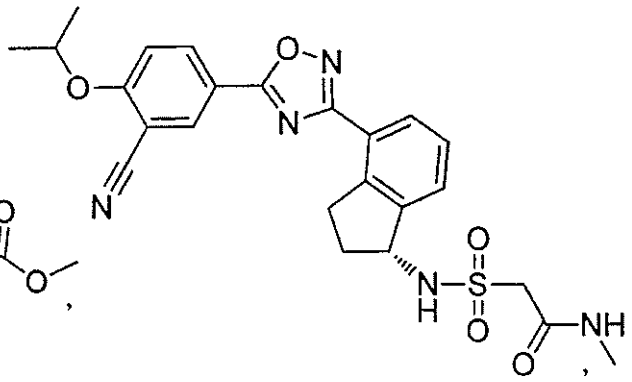

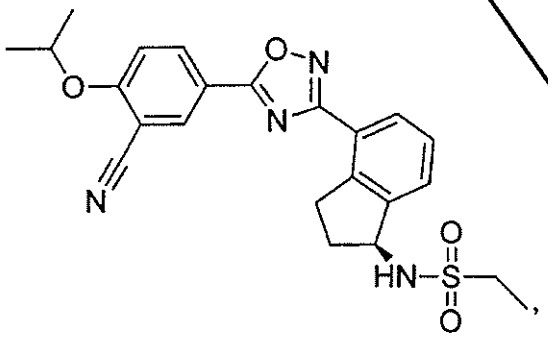

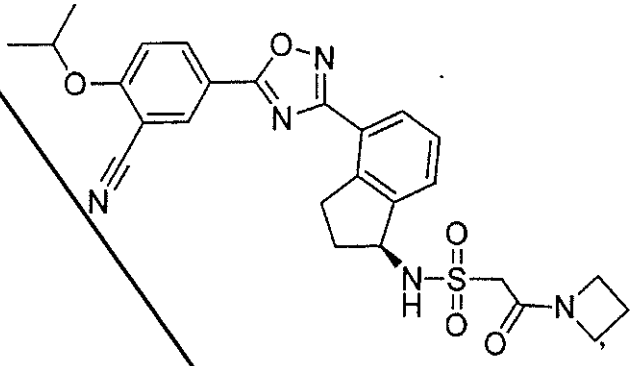

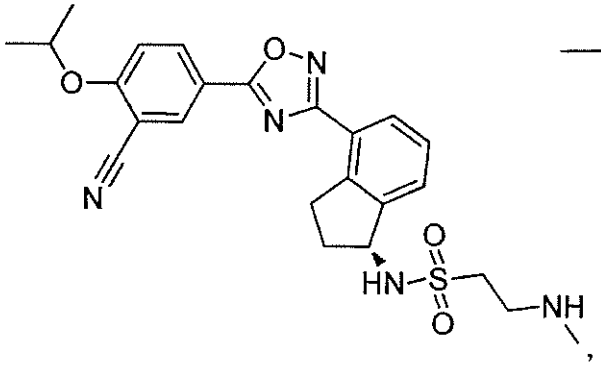

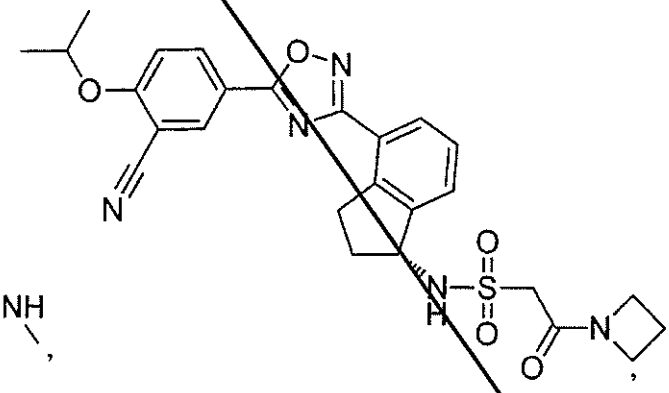

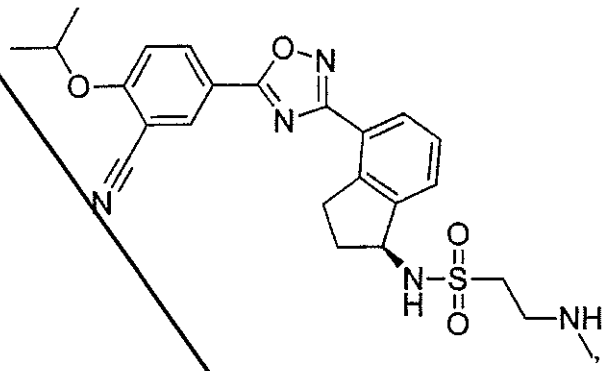

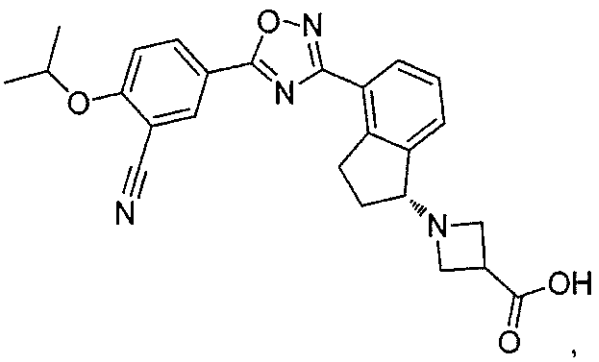

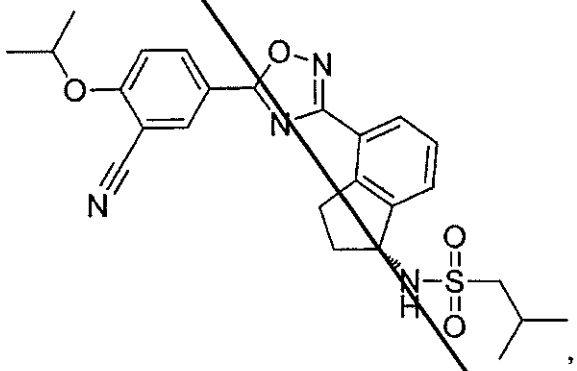

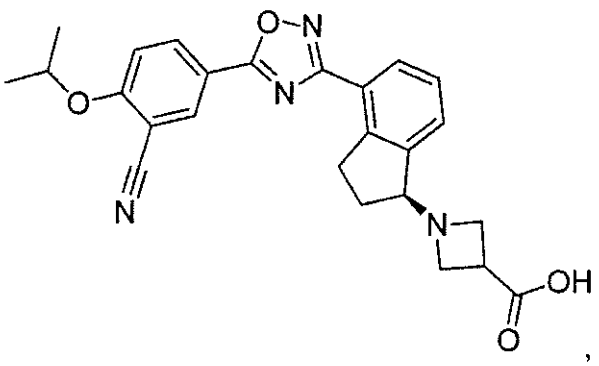

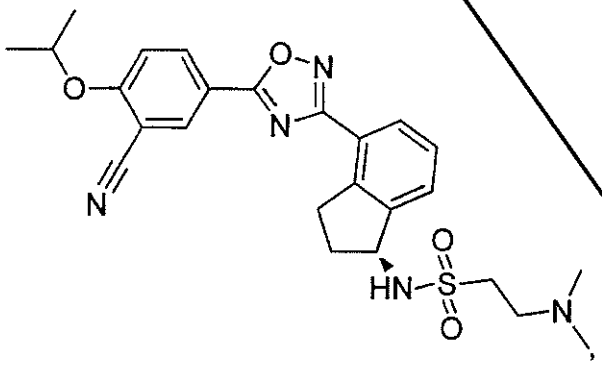

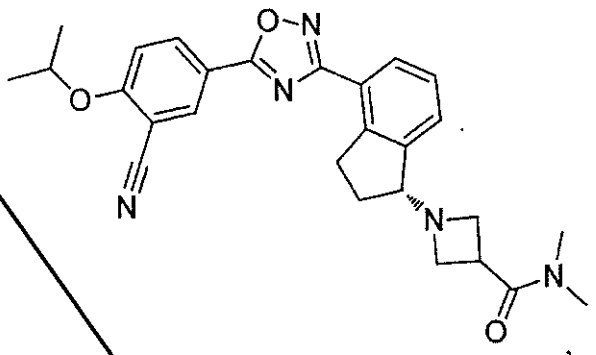

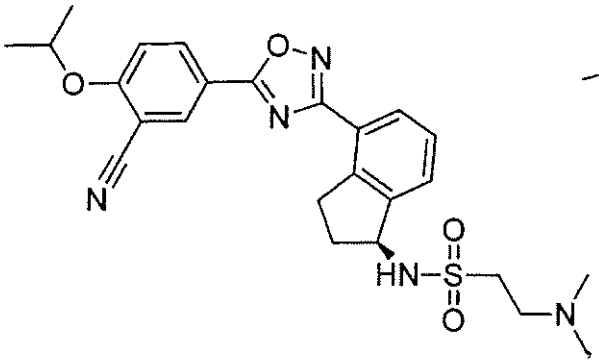

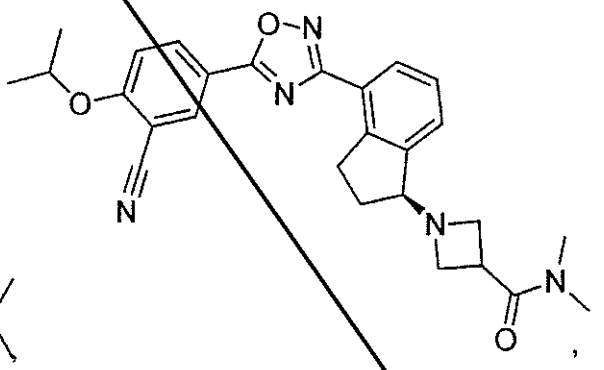

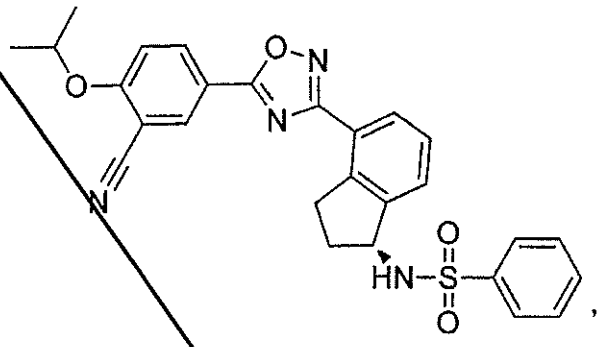

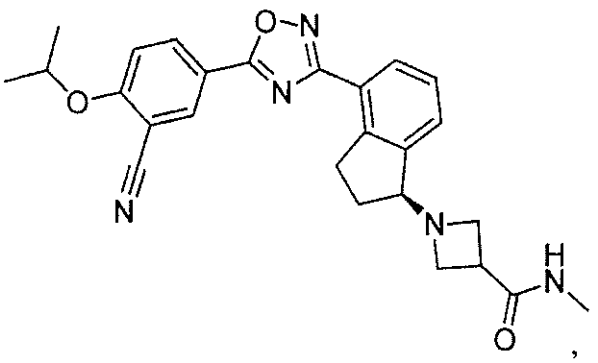

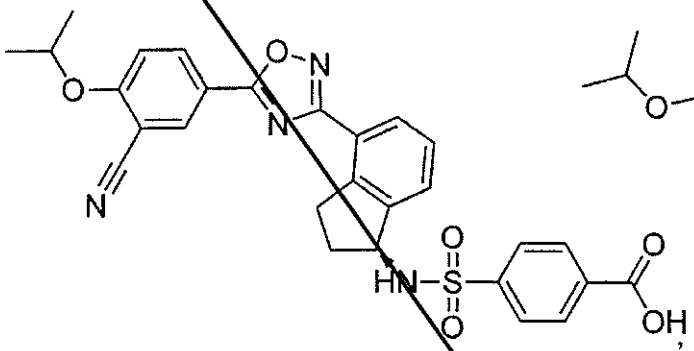

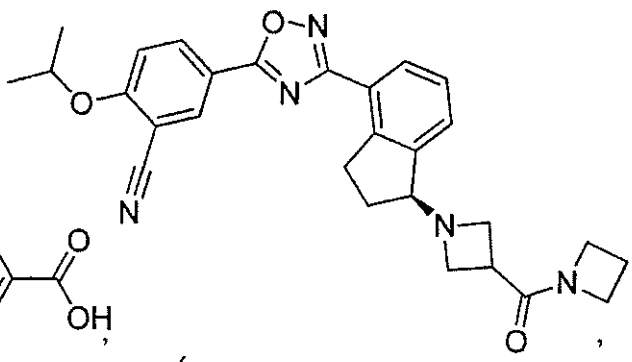

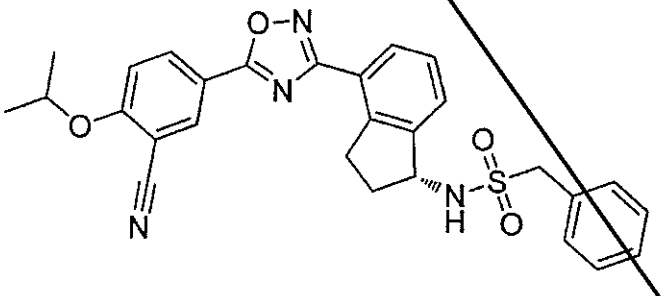

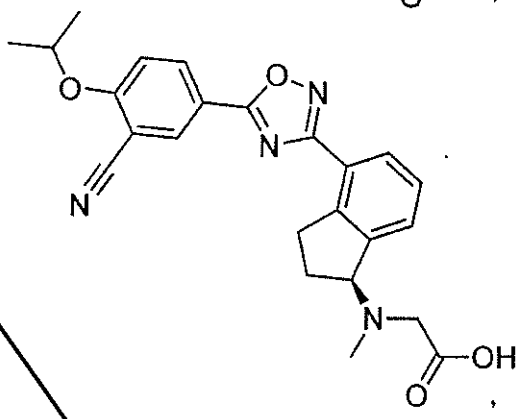

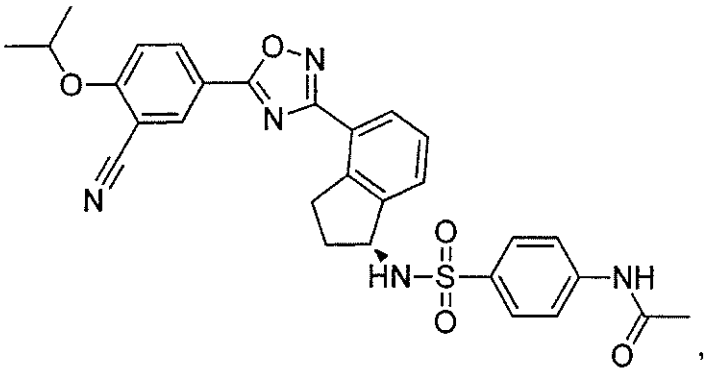

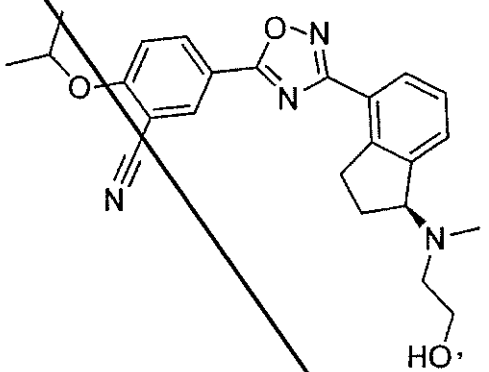

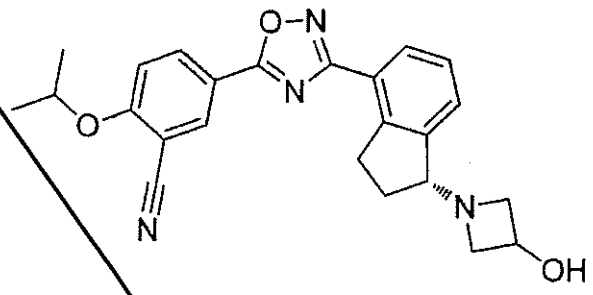
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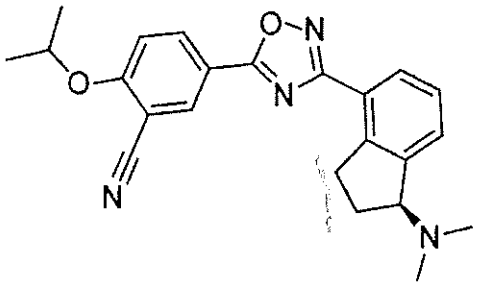
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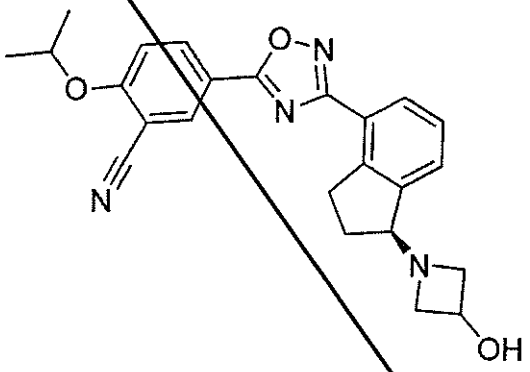
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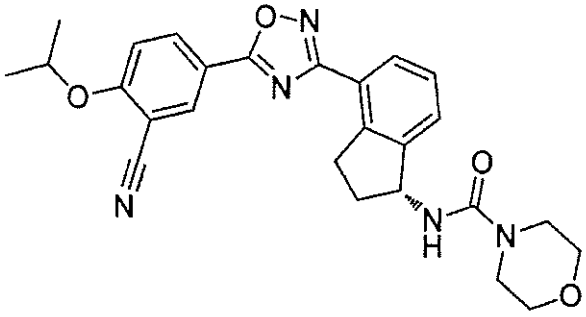
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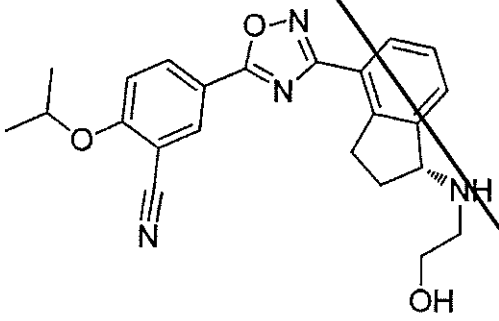
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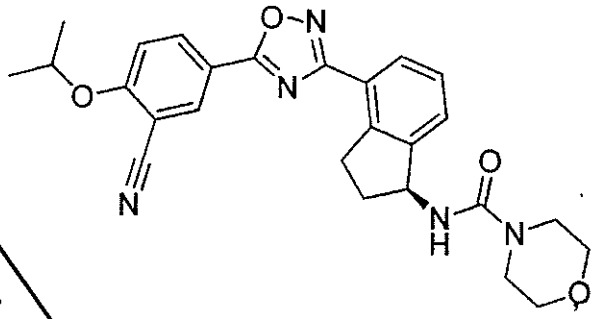
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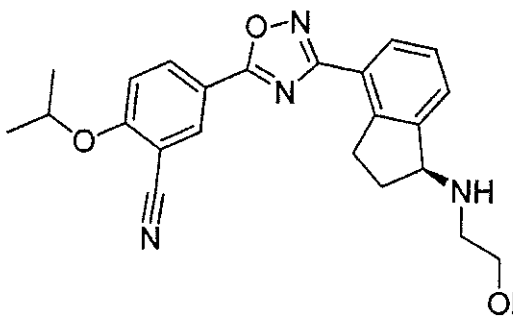
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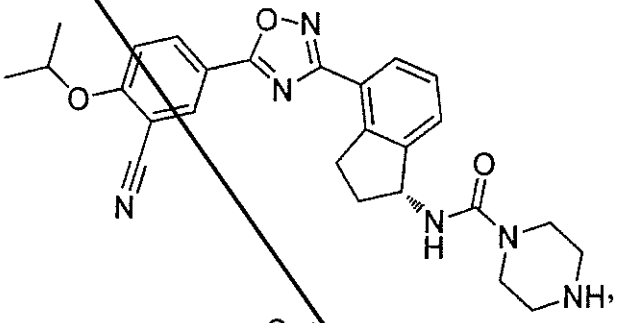
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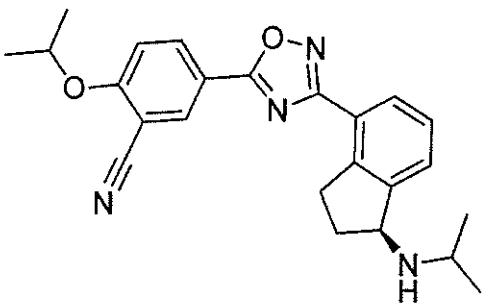
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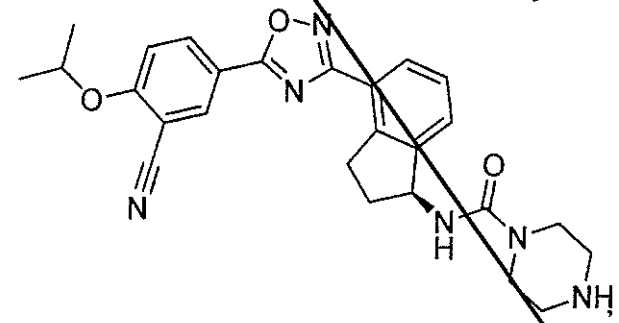
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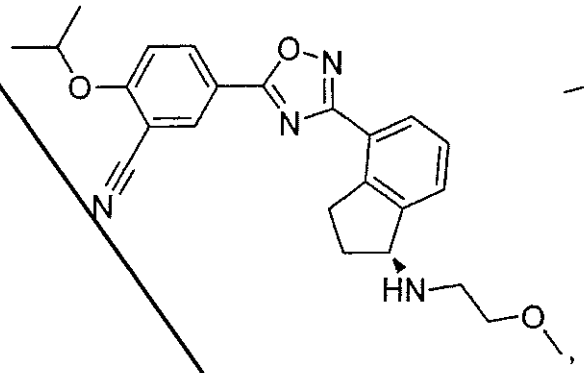

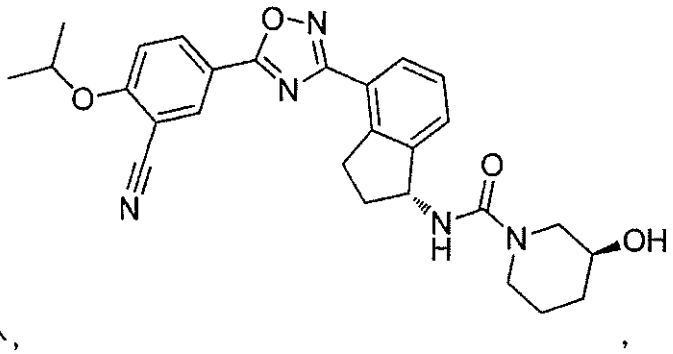

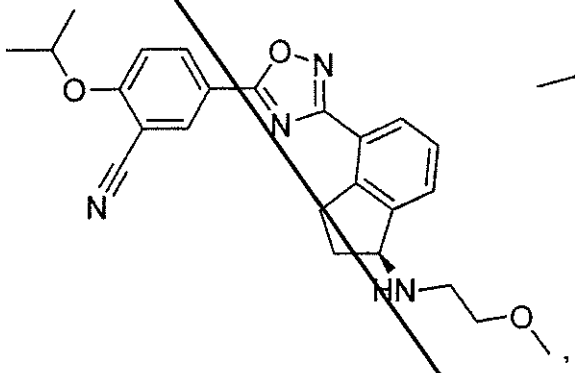

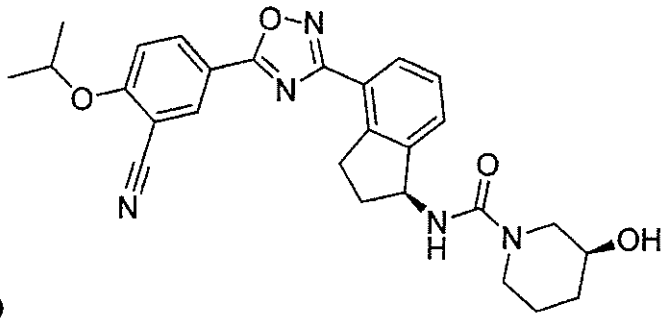

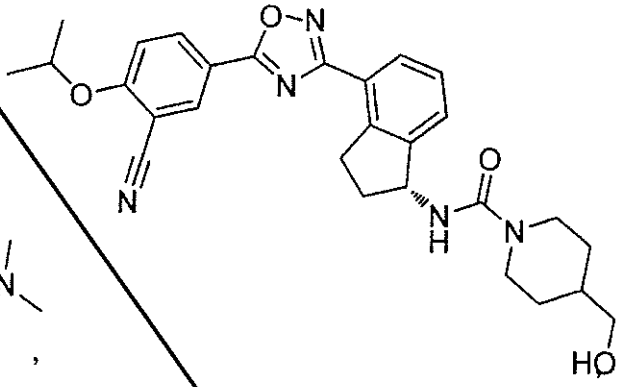

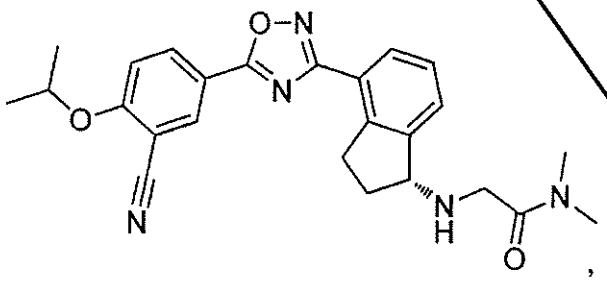

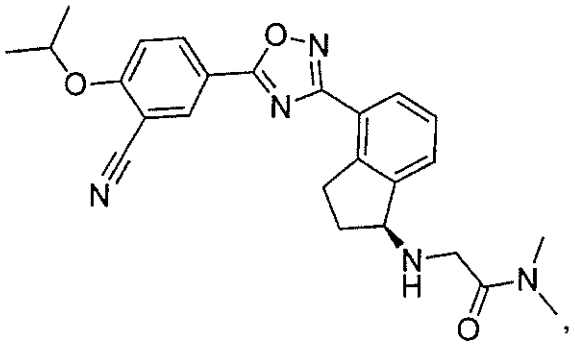

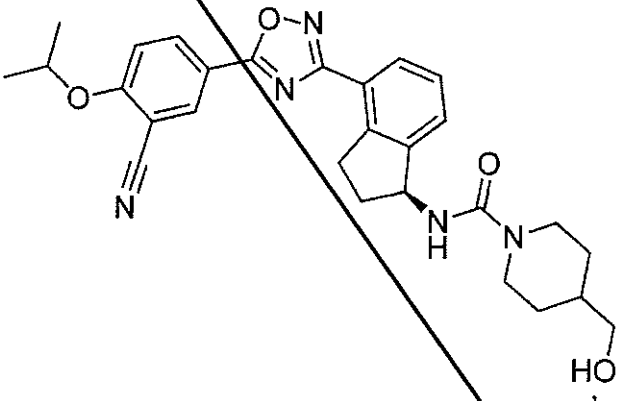

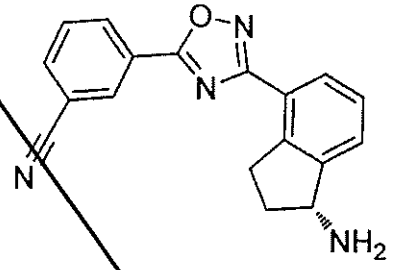

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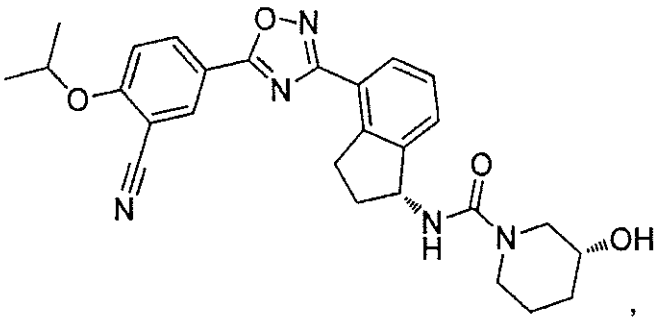

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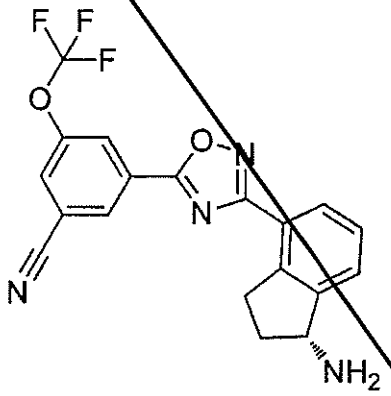

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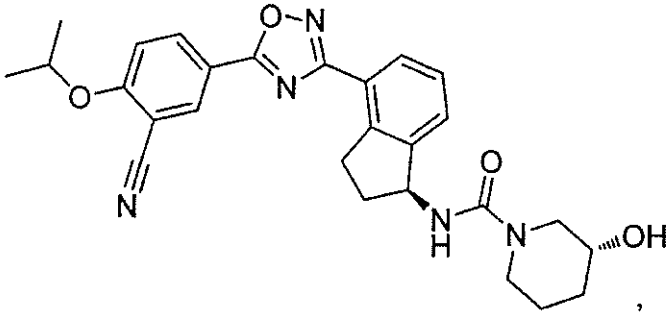

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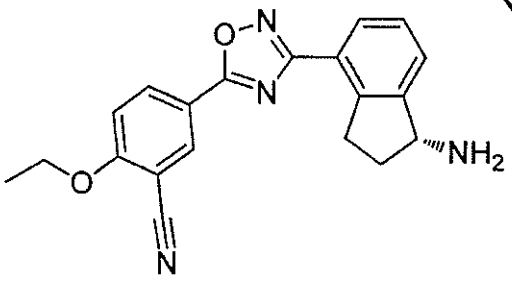

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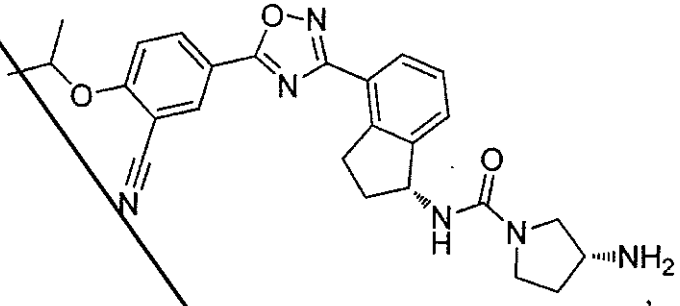

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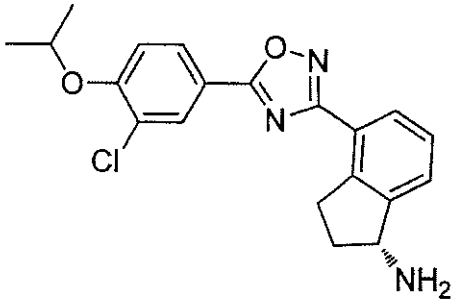

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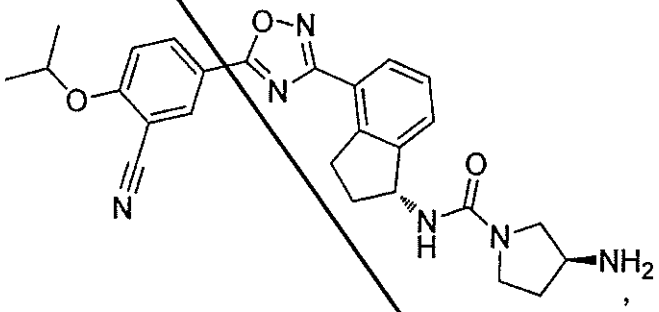

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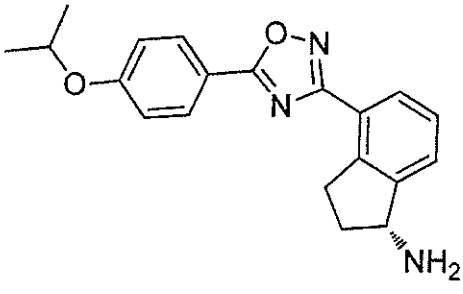

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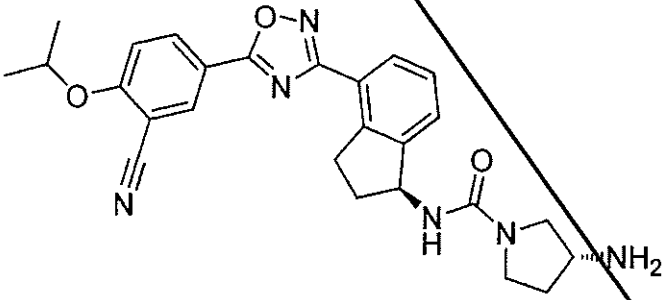

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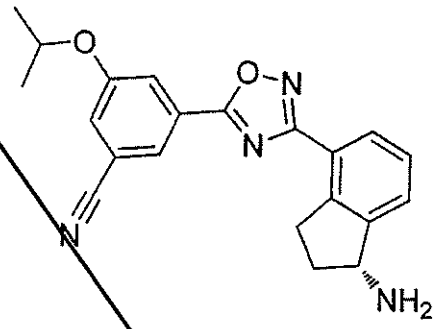

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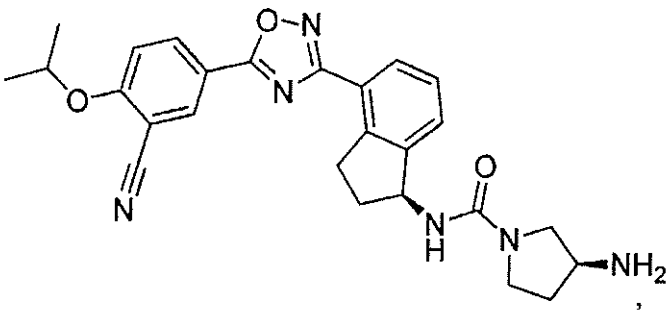

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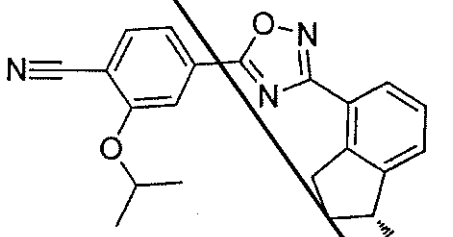

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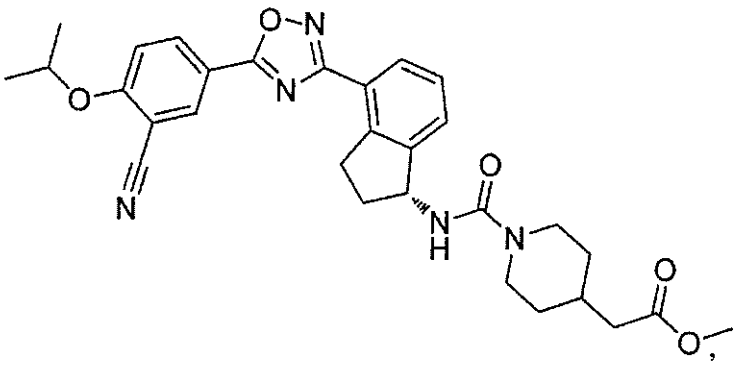

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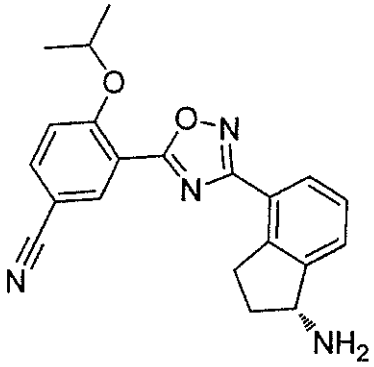

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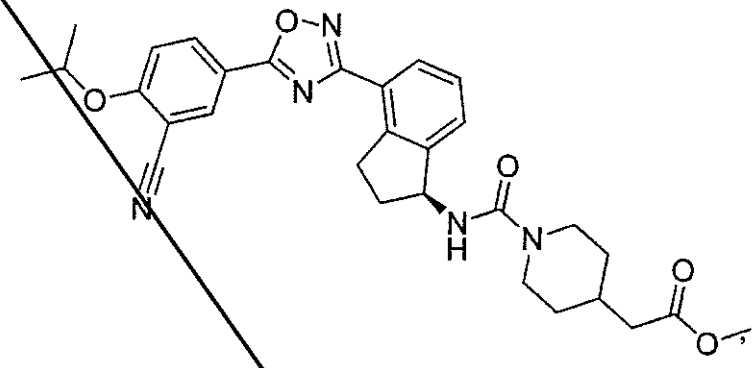

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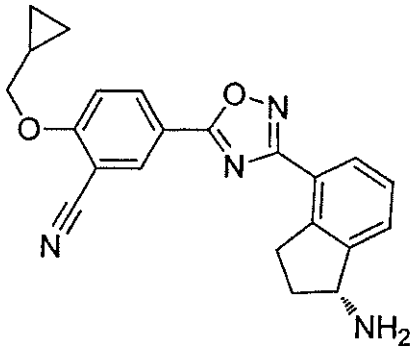

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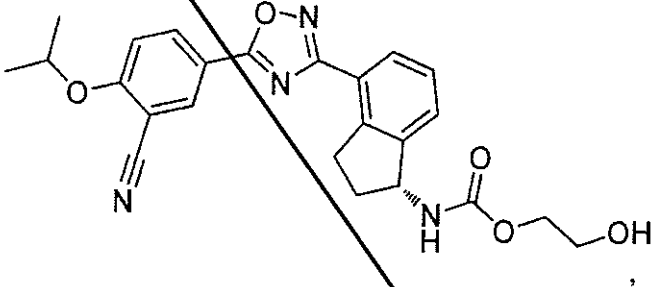

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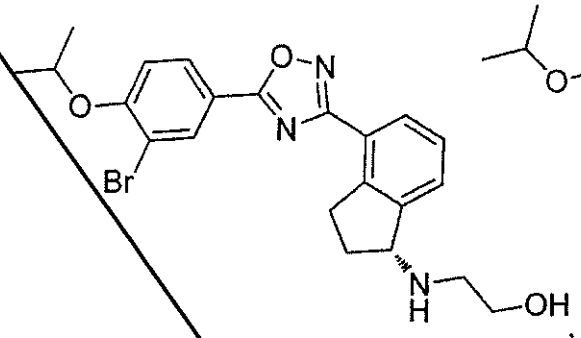

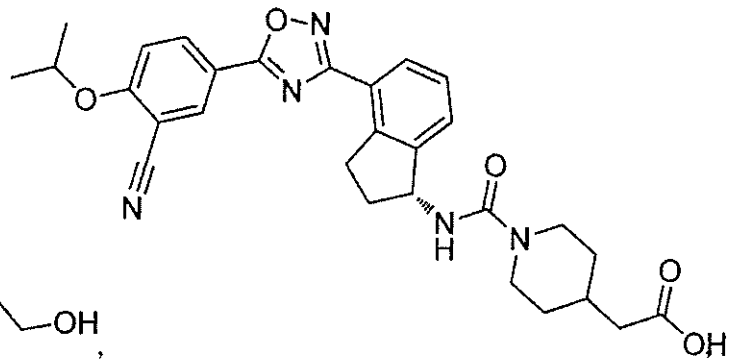

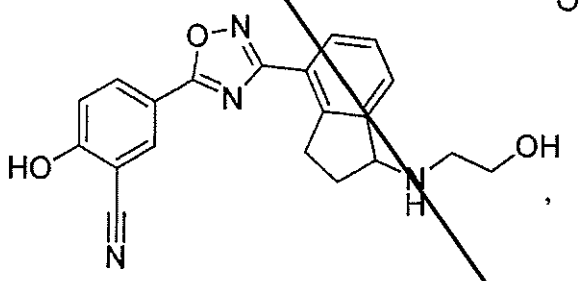

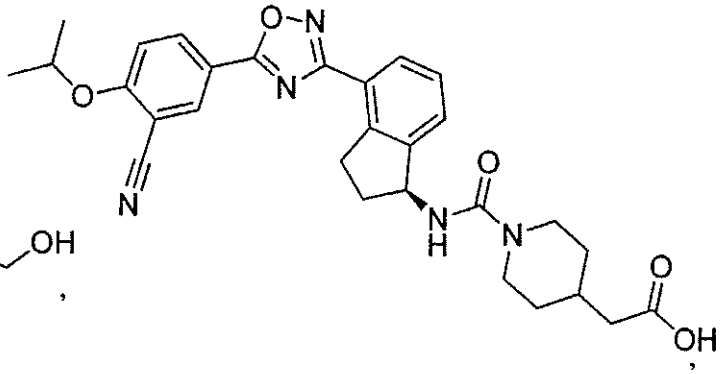

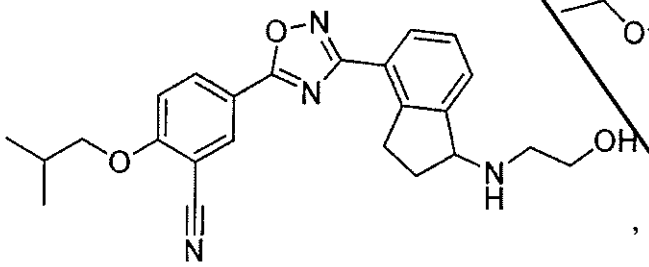

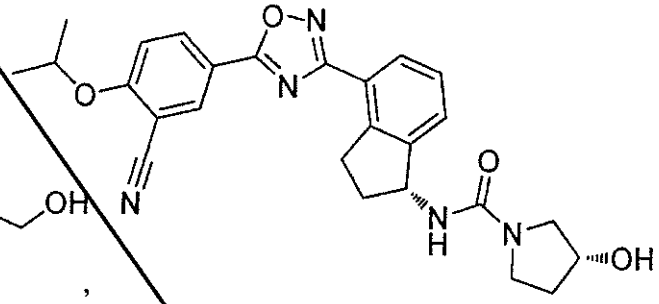

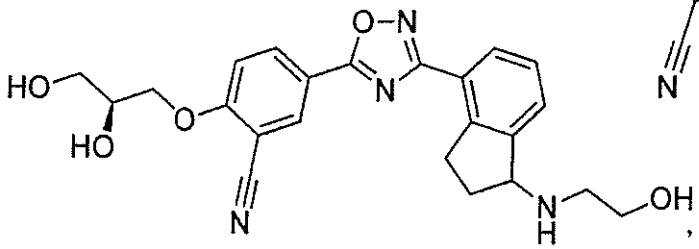

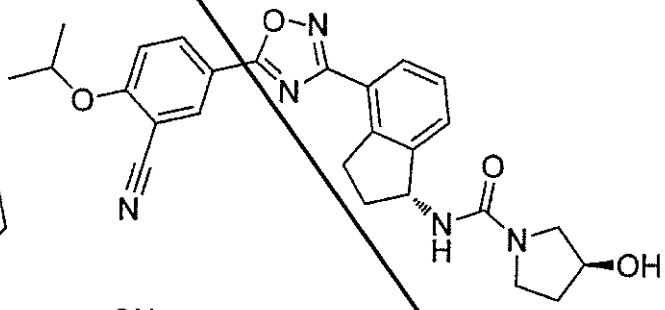

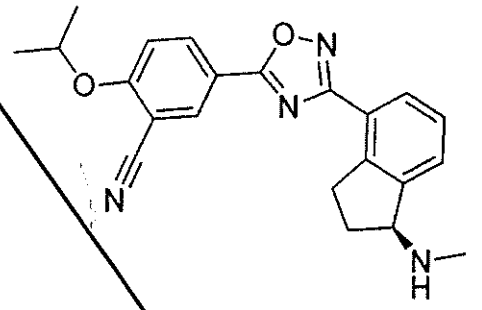
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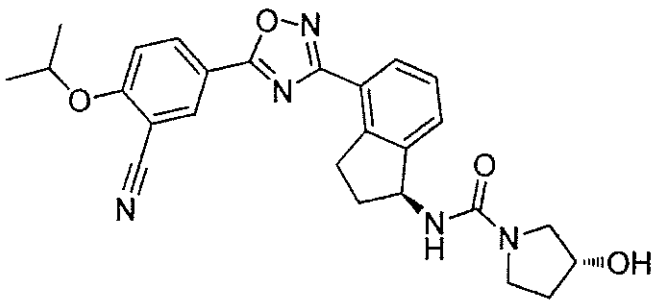
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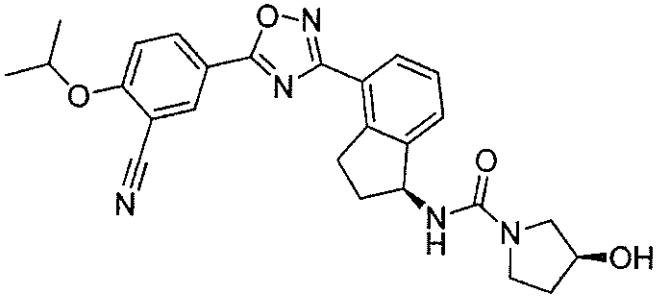
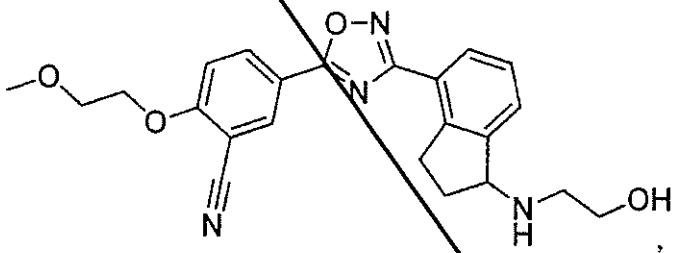
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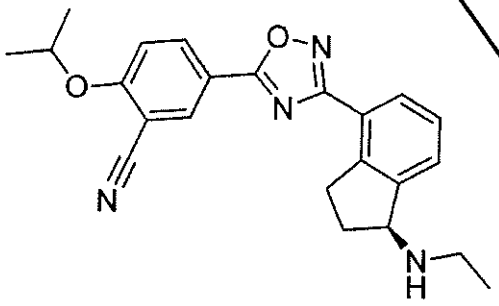
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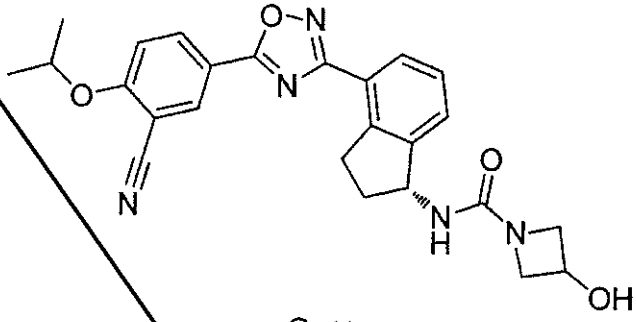
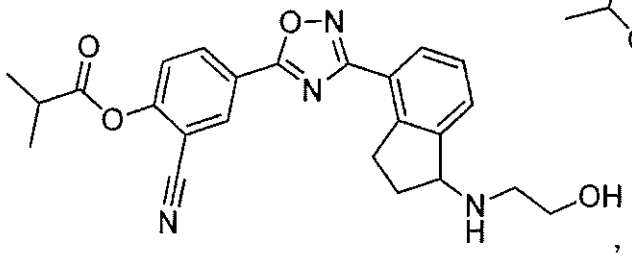
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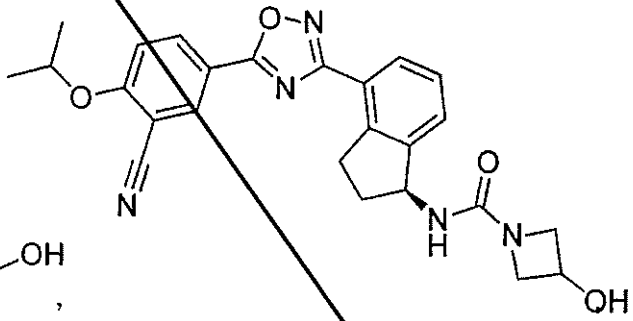
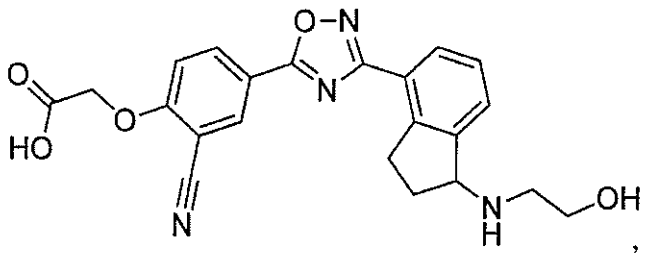
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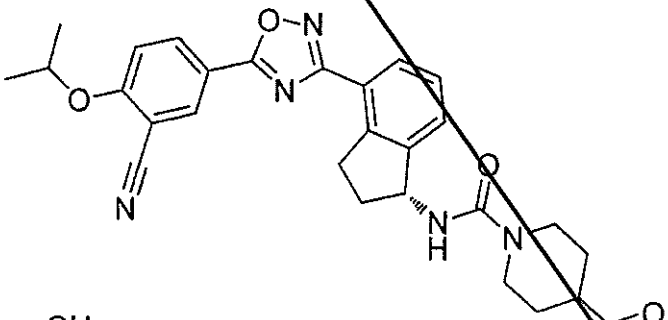

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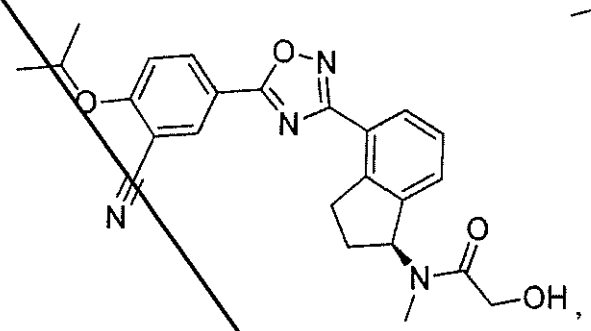

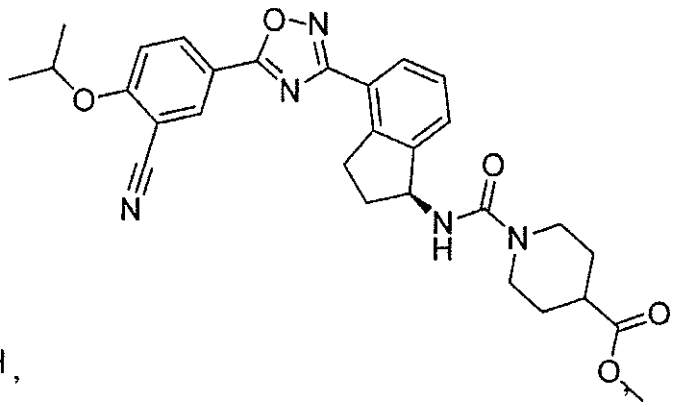

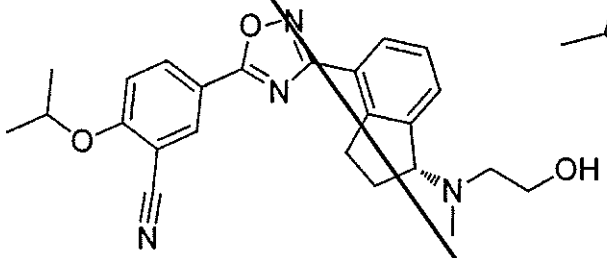

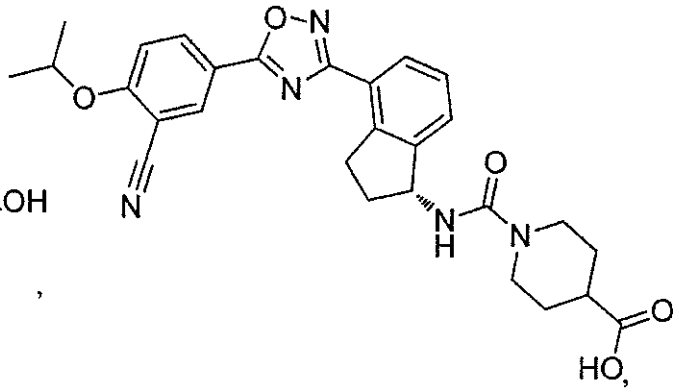

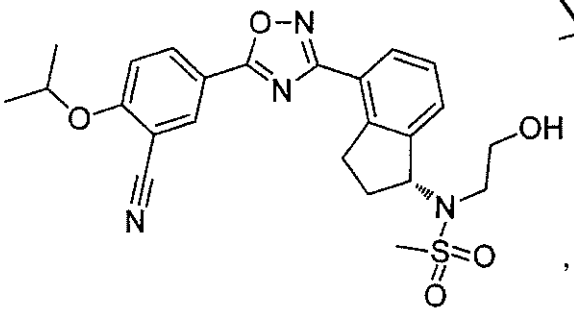

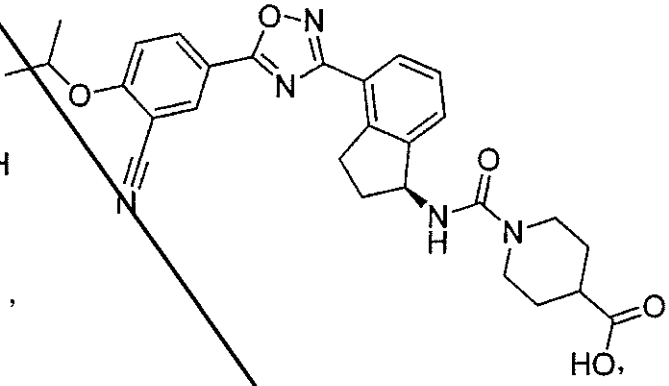

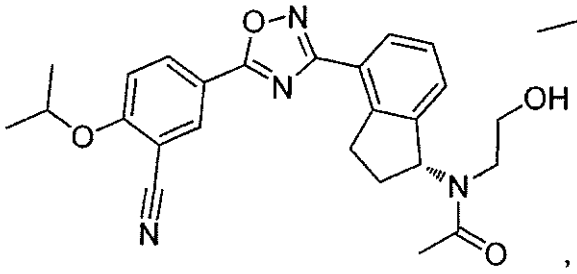

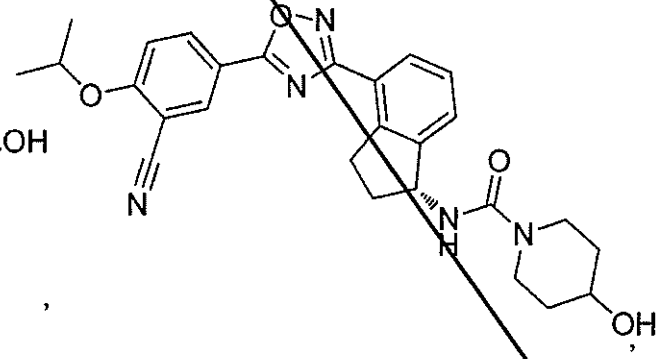

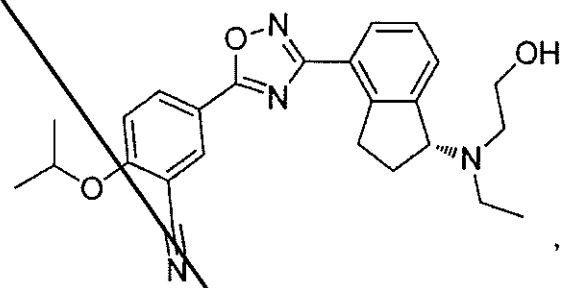
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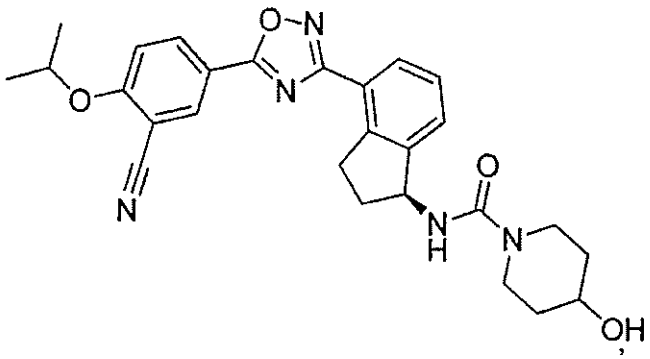
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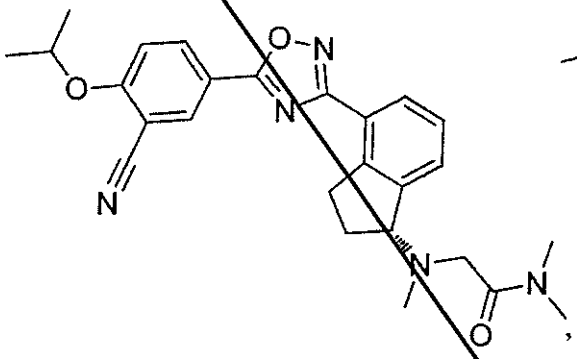
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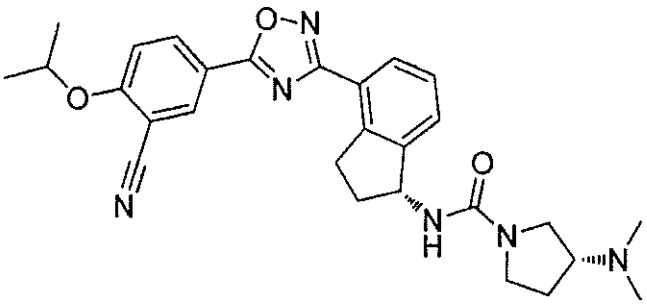
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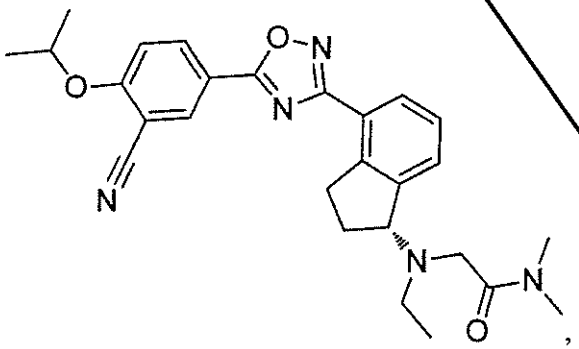
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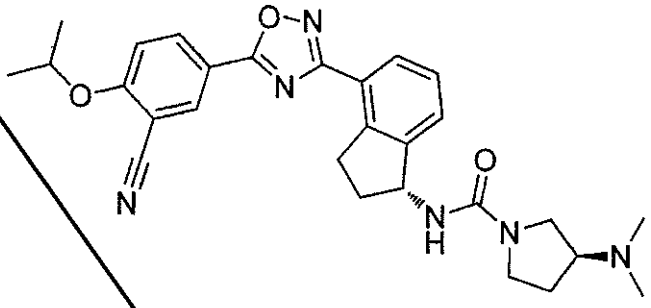
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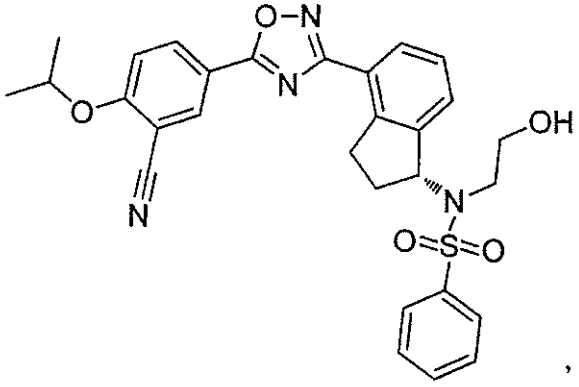
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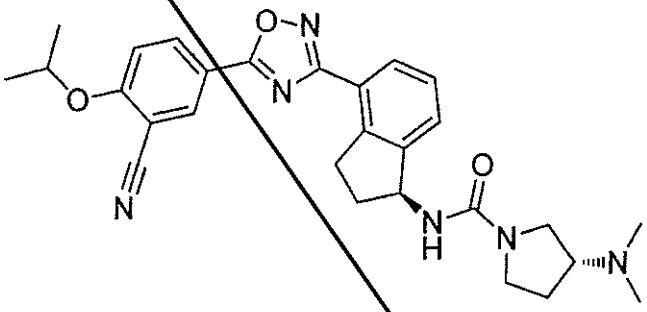
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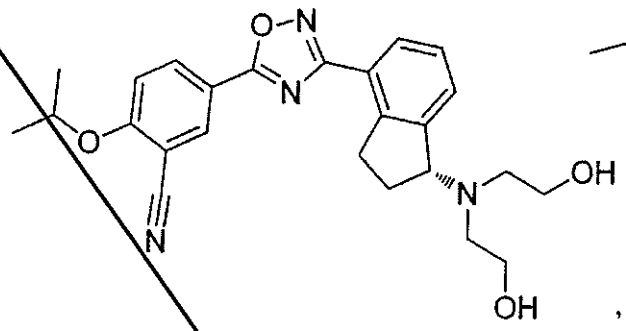

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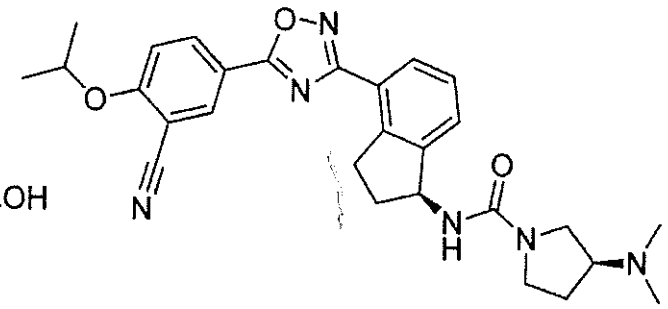

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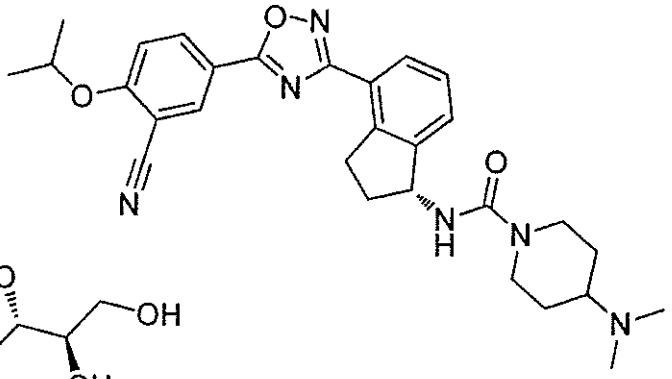

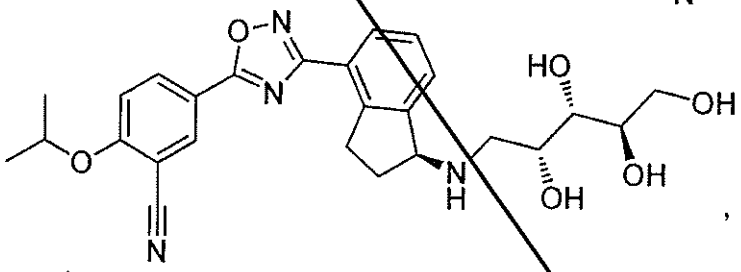

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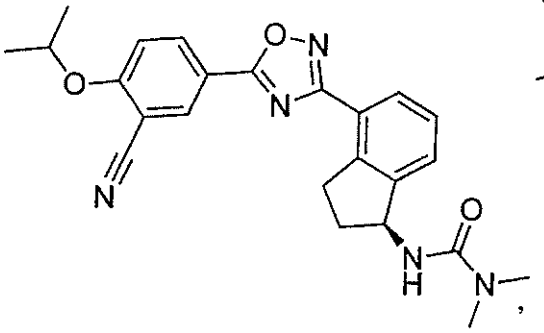

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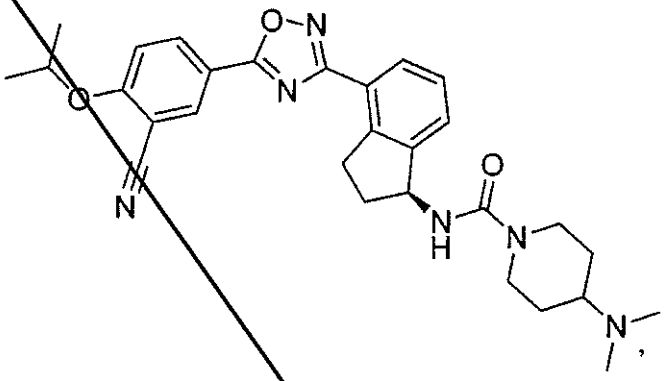

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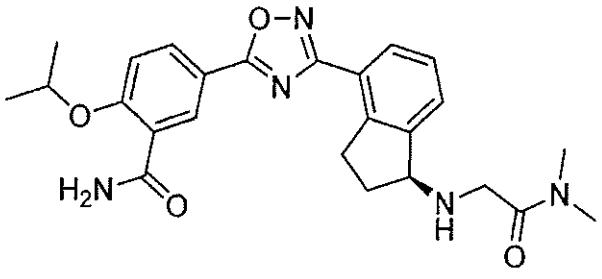

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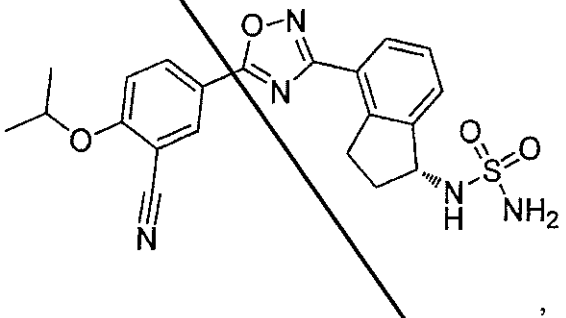

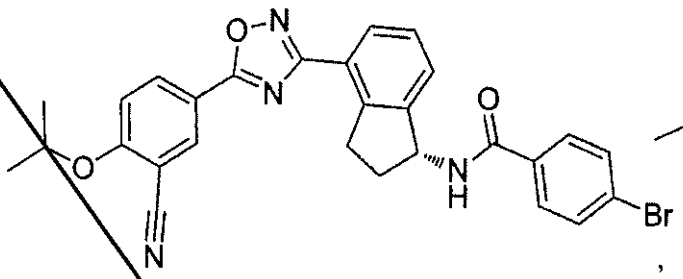

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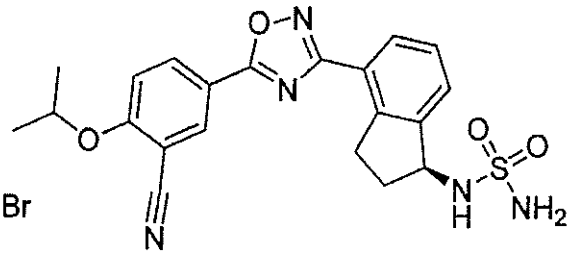

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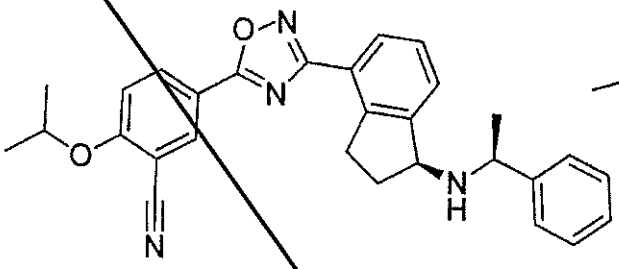

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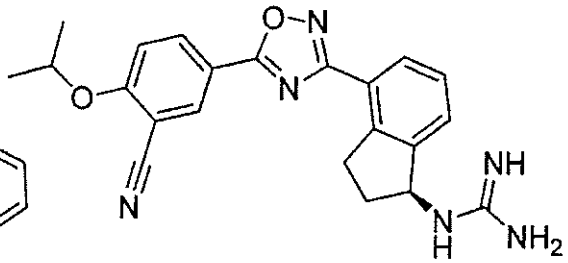

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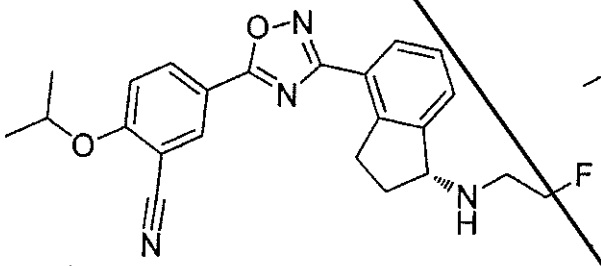

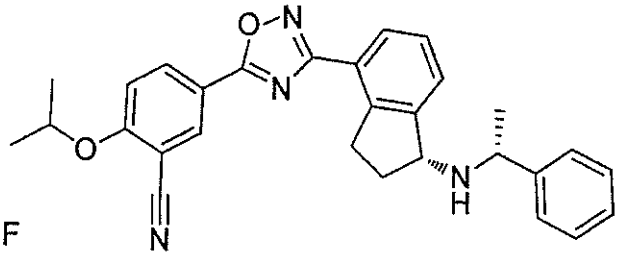

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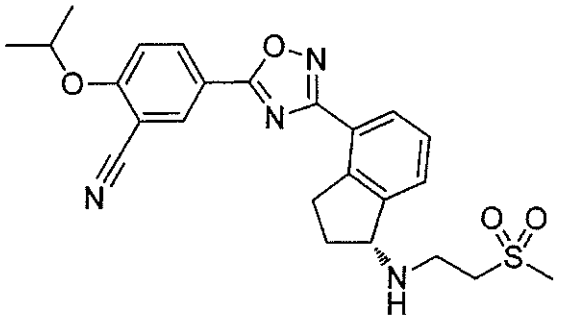

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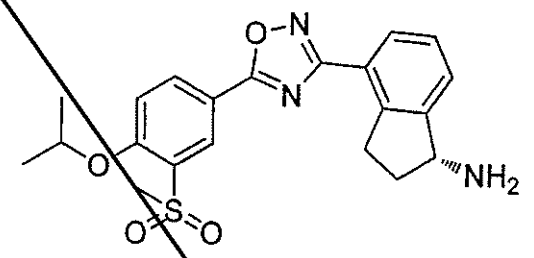

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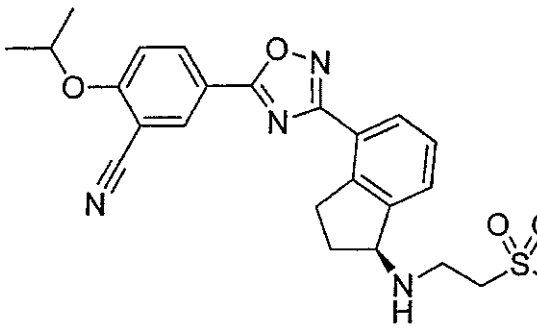

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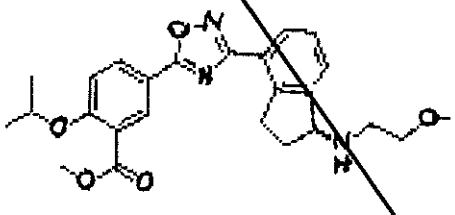
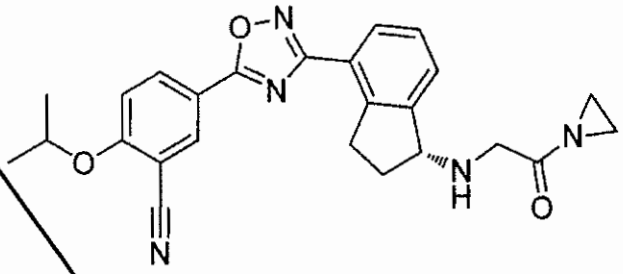
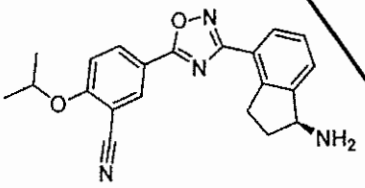




and

or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

35. The compound of claim 34 selected from the group consisting of compounds 50, 86 and 139:



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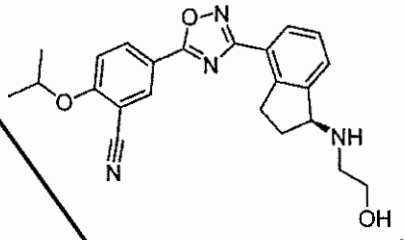

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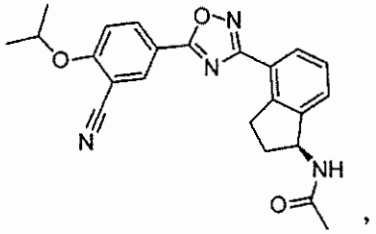
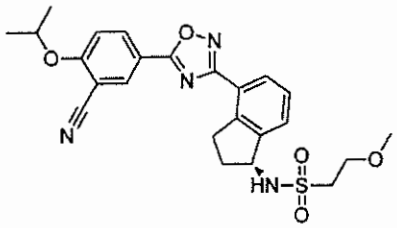


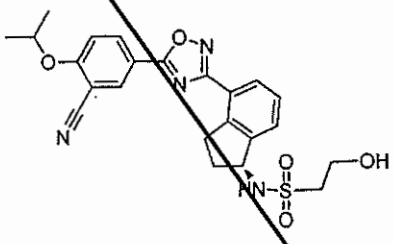
,

or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

36. The compound of claim 34 selected from the group consisting of compounds 163 and, 186:

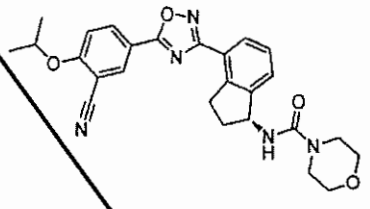
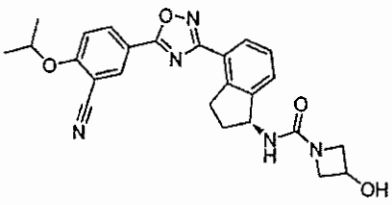


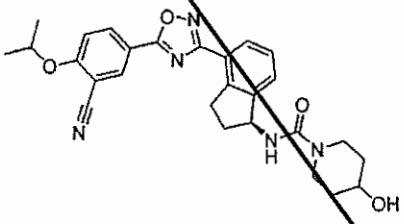
and



or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

37. The compound of claim 34 selected from the group consisting of compounds 211, 234, and 241:

 ,  , and



or a pharmaceutically acceptable salt, ester, prodrug, homolog, hydrate or solvate thereof.

38. A pharmaceutical composition comprising a compound of claims 1-37 and a suitable excipient.

39. A pharmaceutical composition comprising the compound of claims 1-37 and a second medicament.

40. The composition of claim 41 wherein the second medicament is medically indicated for the treatment of multiple sclerosis, transplant rejection, or acute respiratory distress syndrome.

41. The use of a compound of any one of claims 1-37 for preparation of a medicament.

42. A method of activation or agonism of a sphingosine-1-phosphate receptor subtype 1 comprising contacting the receptor subtype 1 with an effective amount of the compound of claims 1-37 or the composition of claims 38-39.

43. The method of claim 42 wherein the compound activates or agonizes the sphingosine-1-phosphate receptor subtype 1 to a greater extent than the compound activates or agonizes a sphingosine-1-phosphate receptor subtype 3.

44. The method of claim 42 wherein the sphingosine-1-phosphate receptor subtype 1 is disposed within a living mammal.

45. A method of treatment of a malcondition in a patient for which activation or agonism of an sphingosine-1-phosphate receptor subtype 1 is medically indicated, comprising administering an effective amount of the compound of claims 1-37 to the patient at a frequency and for a duration of time sufficient to provide a beneficial effect to the patient.

46. The method of claim 45 wherein selective activation or agonism of an S1P subtype 1 receptor with respect to other subtypes of S1P receptor is medically indicated.

47. The method of claim 45 or 46 wherein the malcondition comprises multiple sclerosis, transplant rejection, acute respiratory distress syndrome, ulcerative colitis, influenza, Crohn's disease or adult respiratory distress syndrome.

48. A method for the synthesis of a compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety where the compound is enantiomerically enriched with respect to the chiral carbon, the method comprising the steps of

(i) providing a compound comprising an indane moiety where the ring carbon of the five-membered ring of the indane moiety where chiral substitution is desired is oxo substituted at such carbon;

(ii) reacting such compound with a chiral reagent selected from the group consisting of a Corey Bakshita Shibata-oxazaborolidine and a chiral sulfinamide of the form $RS(=O)NH_2$ where R is selected from the group consisting of t-butyl, branched C_{2-6} alkyl and C_{3-8} cycloalkyl; and

(iii) forming a chiral center at the indane moiety carbon previously bound to the oxo group by either reacting such compound with a suitable reducing agent along with the chiral reagent in step (ii) or reacting the result of the reaction of such compound with a suitable reducing agent.

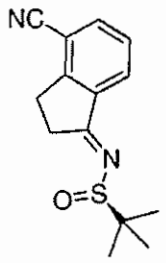
49. The method of claim 48 wherein the chiral reagent is the Corey Bakshita Shibata-oxazaborolidine and the compound comprising an indane moiety is enantiomerically enriched with respect to a carbon-oxygen bond on a ring carbon of the five-membered ring of the indane moiety.

50. The method of claims 48-49 wherein the chiral reagent is (*R*)-(-)-(2)-methyl-CBS-oxazaborolidine or (*S*)-(-)-(2)-methyl-CBS-oxazaborolidine.

51. The method of claim 48 wherein the chiral reagent is $RS(=O)NH_2$ and the compound comprising an indane moiety is enantiomerically enriched with respect to a carbon-nitrogen bond on a ring carbon of the five-membered ring of the indane moiety.

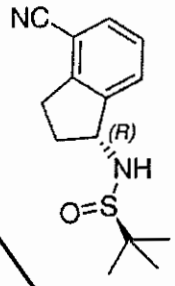
52. The method of claims 48 and 51 wherein the chiral reagent is t-Bu-$S(=O)NH_2$.

53. The method of claims 51-52 wherein the compound comprising an indane moiety provided in step (i) is contacted with the chiral reagent to form in step (ii) Formula **VI**:

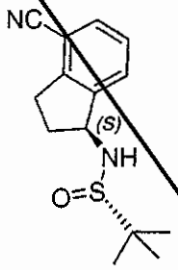


VI.

54. The method of claim 53 wherein a compound of Formula **VII-R** or **VII-S** is formed in step (iii):



VII-R

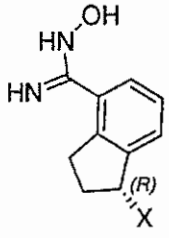


VII-S.

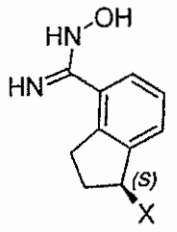
55. The method of claim 48 wherein the compound comprising an indane moiety in step (i) has a cyano substituent on the 4-position of the indane ring.

56. The method of claim 55 wherein the method further comprises the step of

(iv) treating the compound with a chiral center at the indane moiety carbon resulting from step (iii) with a hydroxylamine or a hydroxylamine hydrochloride to convert the cyano substituent to a hydroxyamidine at the 4-position of the indane moiety having the Formula **IV-R** or **IV-S**:



IV-R

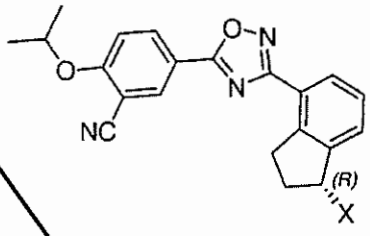


IV-S.

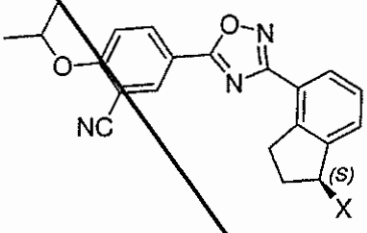
57. The method of claim 56 wherein step (iv) is carried out in the presence of a base.

58. The method of claim 56 wherein the method further comprises the step of

(v) contacting Formula **IV-R** or **IV-S** with substituted benzoic acid and a coupling reagent to form a compound of Formula **V-R** or **V-S**:



V-R

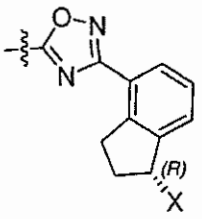


V-S.

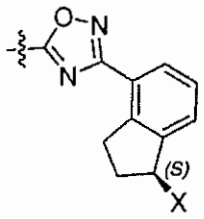
59. The method of claim 58 wherein the coupling reagent is a mixture comprising hydroxybenzotriazole (HOBt) and l-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC).

60. The method of claims 58-59 wherein X is -OR'''.

61. The method of claim 48 wherein the compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety is a compound of the Formula **III-R** or **III-S**:



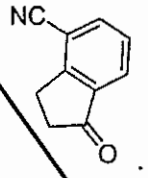
III-R



III-S.

62. The method of claim 61 wherein the compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety is a compound of claims 1-36.

63. The method of claims 48-62 wherein the compound comprising an indane moiety where the ring carbon of the five-membered ring of the indane moiety where chiral substitution is desired is oxo substituted at such carbon is



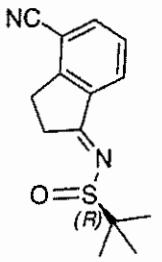
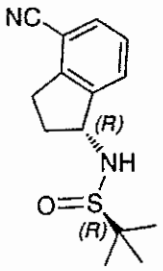
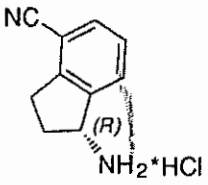
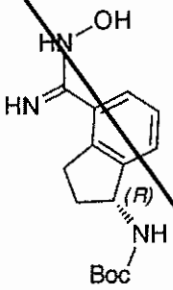
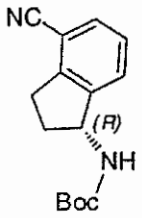
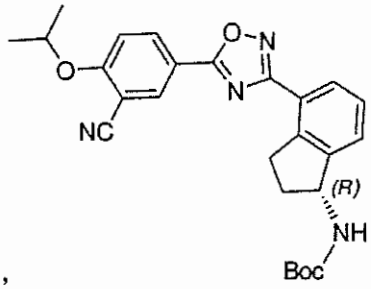
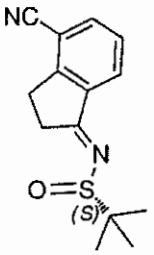
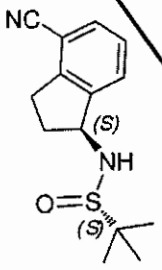
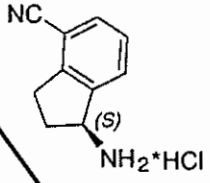
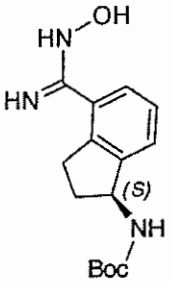
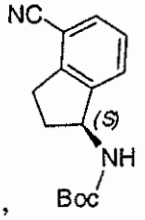
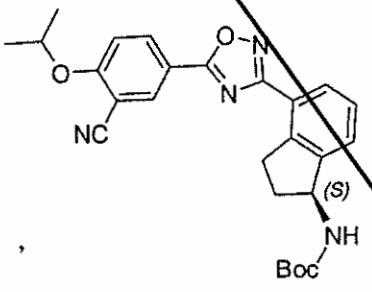
64. The method of claims 48-63 wherein the synthesized compound is enantiomerically enriched at least 90%.

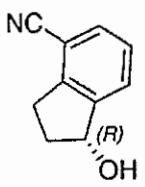
65. The method of claim 64 wherein the synthesized compound is enantiomerically enriched at least 95%.

66. The method of claim 65 wherein the synthesized compound is enantiomerically enriched at least 98%.

67. The method of claim 66 wherein the synthesized compound is enantiomerically enriched at least 99%.

68. A compound selected from the group consisting of:



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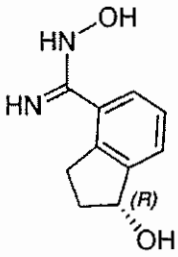

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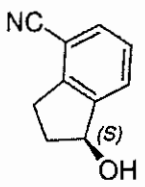

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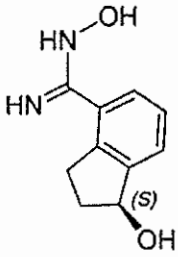

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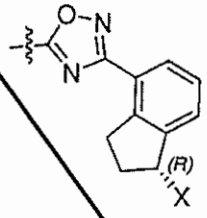
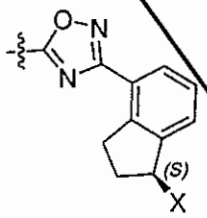
69. A method for the synthesis of a compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety where the compound is enantiomerically enriched with respect to the chiral carbon, the method comprising a step of providing a compound of claim 68.

70. The method of claim 69 wherein the compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety is a compound of the Formula **III-R** or **III-S**:



III-R



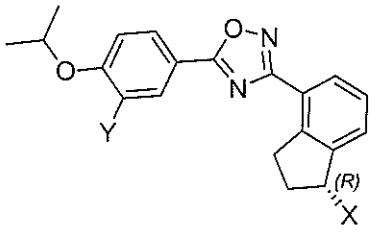
III-S

wherein X is as defined in claim 1.

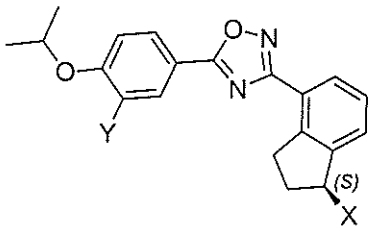
71. The method of claim 70 wherein the compound of the Formula **III-R** or **III-S** is a compound of claims 1-37.

CLAIMS

1. A compound of Formula I-R or Formula I-S or a mixture thereof in any ratio:



I-R



I-S

or pharmaceutically acceptable salt thereof,

wherein

X is $-NH_2$, $-NHC(=O)CH_3$ or $-NHCH_2COOH$, and

Y is –CN.

2. The compound of claim 1 wherein X is $-NH_2$.

3. The compound of claim 1 wherein X is $-NHC(=O)CH_3$.

4. The compound of claim 1 wherein X is $-NHCH_2COOH$.

5. The compound of claim 1 wherein the compound is a racemic mixture of Formula I-R and Formula I-S.

6. The compound of claim 1 wherein the compound is enriched in Formula I-R compared to Formula I-S.

7. The compound of claim 6 wherein the compound is a substantially enantiomerically pure form of Formula I-R.

8. The compound of claim 7 wherein the level of enrichment of Formula I-R with respect to Formula I-S is at least 95%.

9. The compound of claim 7 wherein the level of enrichment of Formula I-R with respect to Formula I-S is at least 99%.

10. The compound of claim 1 wherein the compound is enriched in Formula I-S compared to Formula I-R.

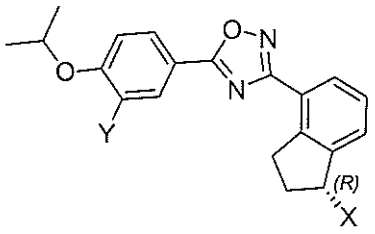
11. The compound of claim 10 wherein the compound is a substantially enantiomerically pure form of Formula I-S.

12. The compound of claim 11 wherein the level of enrichment of Formula I-S with respect to Formula I-R is at least 95%.

13. The compound of claim 11 wherein the level of enrichment of Formula I-S with respect to Formula I-R is at least 99%.

14. A composition comprising a compound of any one of claims 1-13 in combination with a pharmaceutically acceptable carrier or diluent.

15. An isolated optical isomer of Formula I-R:



I-R

or pharmaceutically acceptable salt thereof,

wherein

X is $-NH_2$, $-NHC(=O)CH_3$ or $-NHCH_2COOH$, and

Y is –CN.

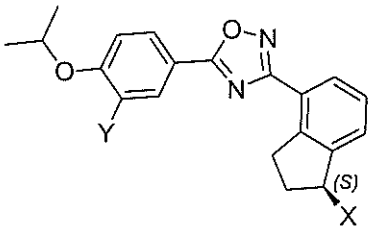
16. The isomer of claim 15 wherein X is $-NH_2$.

17. The isomer of claim 15 wherein X is $-NHC(=O)CH_3$.

18. The isomer of claim 15 wherein X is $-NHCH_2COOH$.

19. A composition comprising an isomer of any one of claims 15-18 in combination with a pharmaceutically acceptable carrier or diluent.

20. An isolated optical isomer of Formula I-S:



I-S

or pharmaceutically acceptable salt thereof,

wherein

X is $-NH_2$, $-NHC(=O)CH_3$ or $-NHCH_2COOH$, and

Y is –CN.

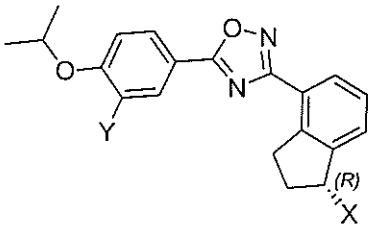
21. The isomer of claim 20 wherein X is $-NH_2$.

22. The isomer of claim 20 wherein X is $-NHC(=O)CH_3$.

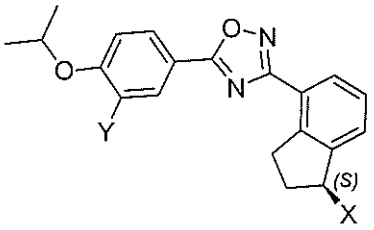
23. The isomer of claim 20 wherein X is $-NHCH_2COOH$.

24. A composition comprising an isomer of any one of claims 20-23 in combination with a pharmaceutically acceptable carrier or diluent.

25. Use of an effective amount of a compound of Formula I-R or Formula I-S, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammatory bowel disease (IBD) in a patient, wherein Formula I-R and Formula I-S are:



I-R



I-S

wherein

X is $-NH_2$,$-NHCH_2CH_2OH$, $-NHC(=O)CH_3$ or $-NHCH_2COOH$, and

Y is –CN.

26. The use of claim 25 wherein X is $-NH_2$.

27. The use of claim 25 wherein X is $-NHCH_2CH_2OH$.

28. The use of claim 25 wherein X is -NHC(=O)CH_3.

29. The use of claim 25 wherein X is –$NHCH_2COOH$.

30. The use of any one of claims 26 to 29 wherein the compound is a racemic mixture of Formula I-R and Formula I-S.

31. The use of any one of claims 26 to 29 wherein the compound is enriched in Formula I-R compared to Formula I-S.

32. The use of claim 31 wherein the compound is a substantially enantiomerically pure form of Formula I-R.

33. The use of claim 32 wherein the level of enrichment of Formula I-R with respect to Formula I-S is at least 95%.

34. The use of claim 32 wherein the level of enrichment of Formula I-R with respect to Formula I-S is at least 99%.

35. The use of claim 25 wherein the compound is enriched in Formula I-S compared to Formula I-R.

36. The use of claim 35 wherein the compound is a substantially enantiomerically pure form of Formula I-S.

37. The use of claim 36 wherein the level of enrichment of Formula I-S with respect to Formula I-R is at least 95%.

38. The use of claim 36 wherein the level of enrichment of Formula I-S with respect to Formula I-R is at least 99%.

39. The use of any one of claims 25-38 wherein the IBD is ulcerative colitis.

40. The use of any one of claims 25-38 wherein the IBD is Crohn's disease.