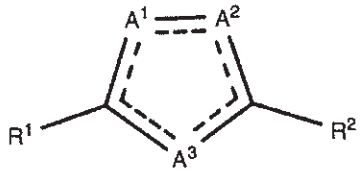
We claim:

1. A compound of Formula (I) or a pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof:



(I)

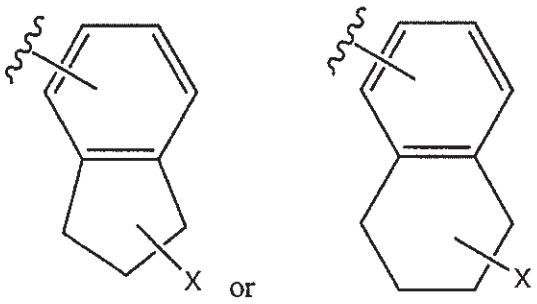
wherein

a dashed line signifies that a single bond or a double bond can be present, provided that there are two double bonds and three single bonds in the ring comprising A^1, A^2, and A^3;

A^1, A^2, and A^3 each independently is C or S or N; provided that one of A^1, A^2, and A^3 is S;

R^1 is di-substituted phenyl or di-substituted pyridinyl where the phenyl and pyridinyl substituents are each independently selected from the group consisting of halo, nitro, cyano, perfluromethyl, fluorinated methyl, and C_{1-4}-alkoxy; provided that if R^1 is di-substituted phenyl, such phenyl is para-substituted with C_{1-4}-alkoxy;

R^2 is



wherein a wavy line indicates a point of attachment;

X is –NR′R″ or -OR‴;

R′ is H, C_{1-4} alkyl, n-hydroxy C_{1-4} alkyl, -SO_2-R^3, or -CO-R^3;

R″ is H, -SO_2-R^5 , C_{1-4} alkyl optionally substituted with 1 or more R^4, or a ring moiety optionally substituted with R^6 wherein such ring moiety is piperidinyl, cyclohexyl, morpholinyl, thiazolyl, pyrazolyl, pyrrolidinyl, imidazolyl, or phenyl;
R‴ is H, C_{1-4} alkyl, or -CO-R^3

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, -$(CH_2)_m$-$COOR^3$, -$N(R^3R^3)$, and -$(CH_2)_m$-CO-$N(R^7R^7)$;
each R^3 is independently C_{1-4} alkyl or H;

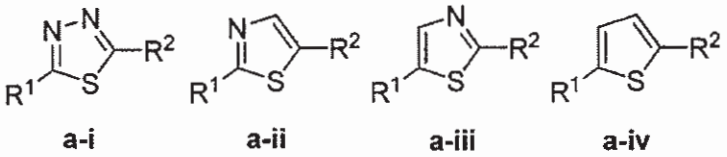
each R^4 is independently H, halo, OH, oxo, =NH, NH_2, -COOH, F, -NHR^3, -$N(R^7R^7)$,–SO_2-R^3, –SO_2-$N(R^7R^7)$, -$N(R^3)$–SO_2-R^3, -$COOR^3$, -OCO-R^3, -CO-$N(R^7R^7)$, -$N(R^3)$-COR^3, C_{1-3} alkyl, C_{1-3} alkoxy, and a ring moiety optionally substituted with R^6 wherein such ring moiety is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, pyrazolyl, imidazolyl, benzimidazolyl, azetidinyl, cyclobutinyl, or phenyl;

each R^5 is independently R^4, C_{1-4} alkyl, C_{3-6} cycloalkyl, or C_{1-4} alkyl optionally substituted with 1 or more R^4;

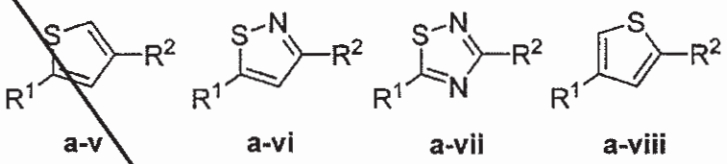
each R^6 is independently halo, OH, -NH_2, -NHR^3, -$N(R^3R^3)$, -COOH, -$COOR^3$, -NHCO-R^3; each R^7 is independently C_{1-4} alkyl or H, or two R^7 taken together with the nitrogen atom to which they are bound form a 4, 5, or 6 membered saturated heterocyclic ring containing 0 or 1 additional heteroatoms where such additional heteroatom is O or N wherein such heterocycle is optionally substituted with –OH, -NH_2, -$N(R^3R^3)$, n-hydroxy C_{1-4} alkyl, -$(CH_2)_m$-COOH, -$(CH_2)_m$-$COOR^3$;

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

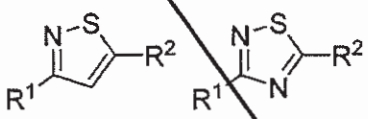
2. The compound of claim 1 wherein the structure of Formula **I** is selected from the group consisting of formulas **a-i** through **a-x**:



a-i **a-ii** **a-iii** **a-iv**



a-v **a-vi** **a-vii** **a-viii**



a-ix **a-x**

3. The compound of claim 1 wherein A^1 is S.

4. The compound of claim 1 wherein A^2 is S.

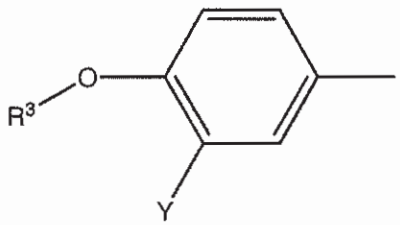
5. The compound of claim 1 wherein A^3 is S.

6. The compound of claim 5 wherein A^1 is N and A^2 is C or N.

7. The compound of claim 6 wherein A^2 is C.

8. The compound of claim 6 wherein A^2 is N.

9. The compound of claims 1-8 wherein R^1 is



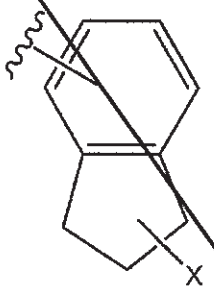
;

R^3 is C_{2-4} alkyl; and Y is –CN, -Cl, I, -O-R^3, -COOH, -COOR^3, or -CF_3.

10. The compound of claim 9 wherein R^3 is isopropyl or ethyl.

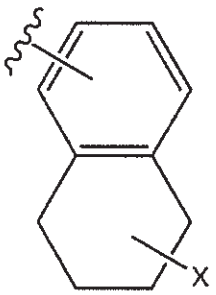
11. The compound of claims 9-10 wherein Y is -CN or –O-C_2H_5.

12. The compound of claims 1-11 wherein R^2 is



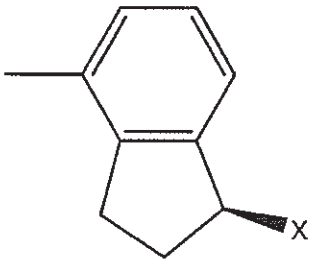
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13. The compound of claims 1-11 wherein R^2 is

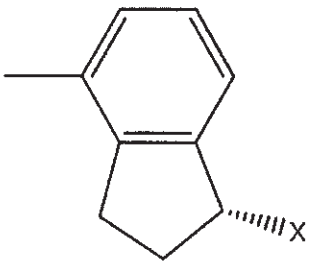


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14. The compound of claim 12 wherein R^2 is

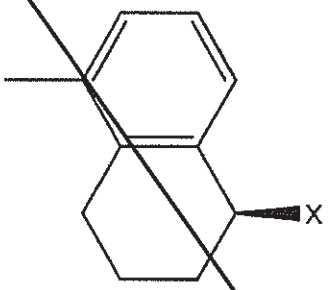


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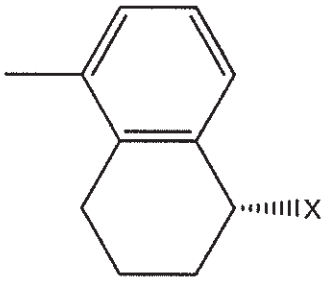


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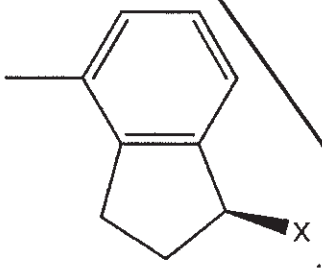
15. The compound of claim13 wherein R^2 is



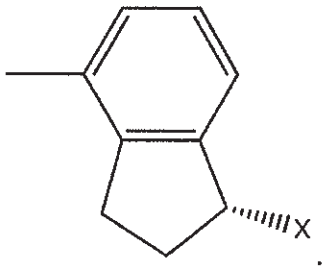
or



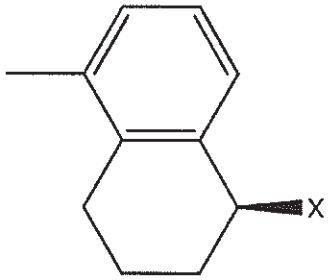
16. The compound of claim 14 wherein R^2 is



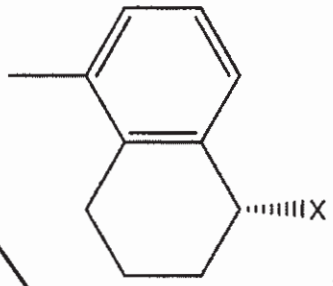
17. The compound of claim 14 wherein R^2 is



18. The compound of claim 15 wherein R^2 is



19. The compound of claim 15 wherein R^2 is

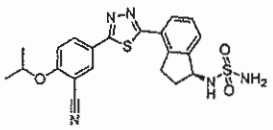
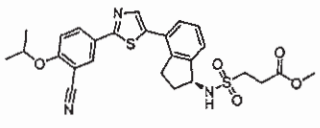
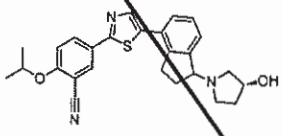


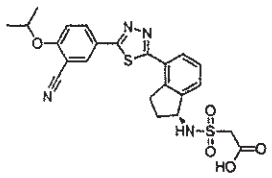
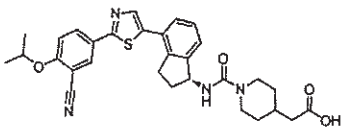
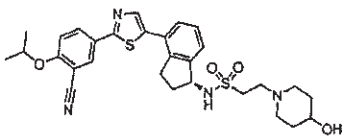
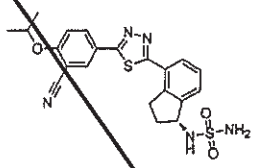
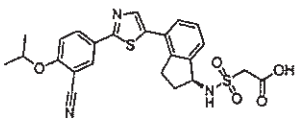
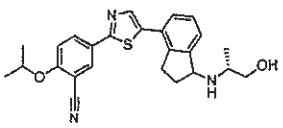
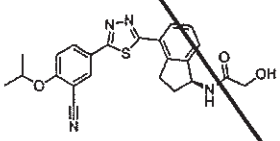
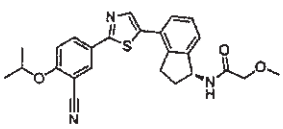
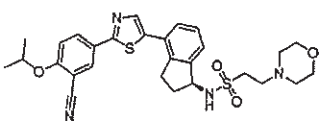
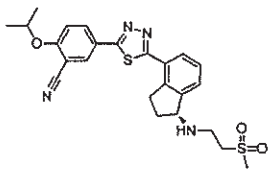
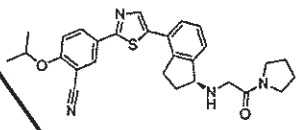
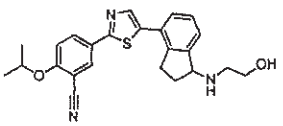
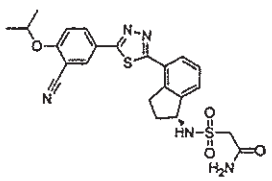
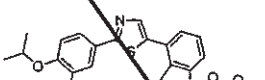
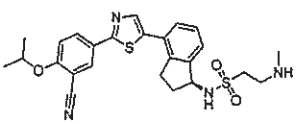
20. The compound of claims 16-19 wherein the compound is substantially enantiomerically pure.
21. The compound of claims 1-20 wherein the compound has an EC_{50} as an S1P receptor subtype 1 agonist which is at least ten times smaller than its EC_{50} as an agonist of a mutant S1P receptor subtype 1 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.
22. The compound of claim 21 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.
23. The compound of claims 1-22 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.

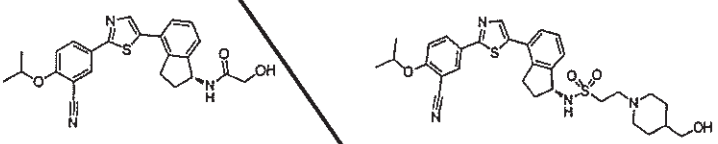
24 The compound of claim 23 wherein the therapeutic index is at least 10.

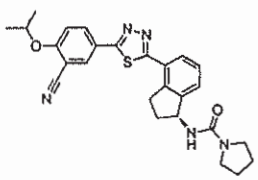
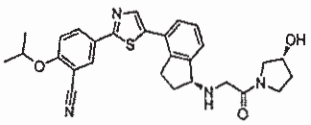
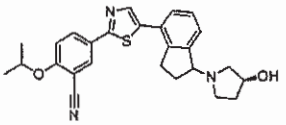
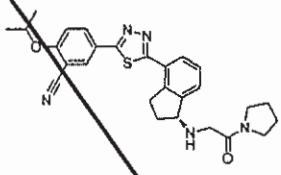
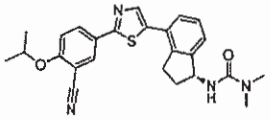
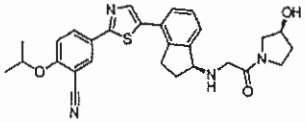
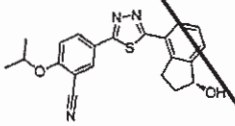
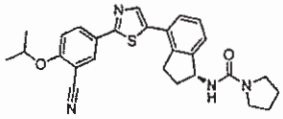
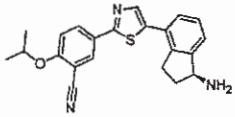
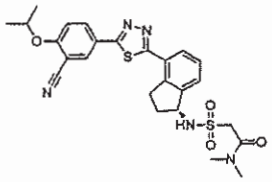
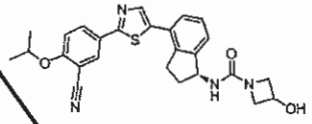
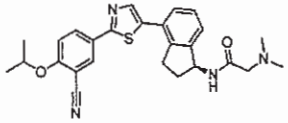
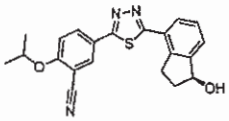
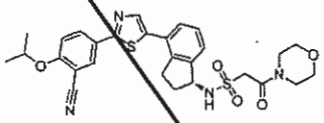
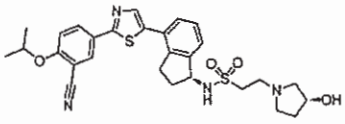
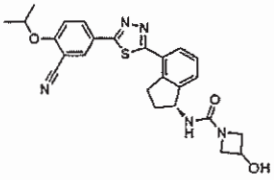
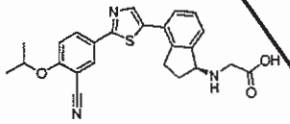
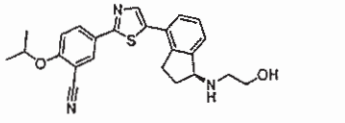
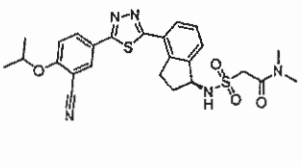
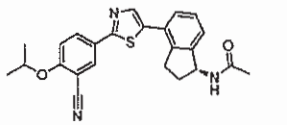
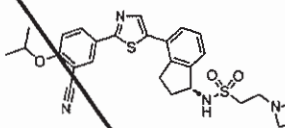
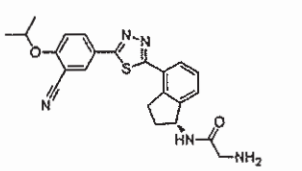
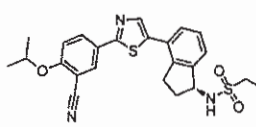
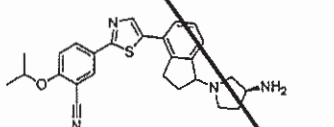
25. The compound of claim 23 wherein the therapeutic index is at least 20.
26. The compound of claims 23-25 wherein the therapeutic index for the compound is greater than the therapeutic index for the enantiomer of the compound.
27. The compound of claim 26 wherein the therapeutic index for the compound is at least 150% of the therapeutic index for the enantiomer of the compound.
28. The compound of claims 1-27 wherein Y is Cl.
29. The compound of claims 1-27 wherein Y is CF_3.

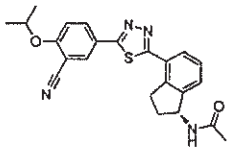
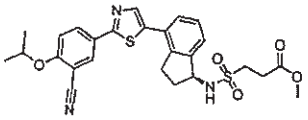
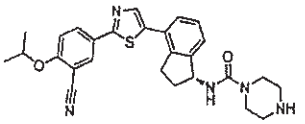
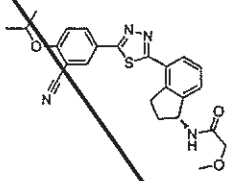
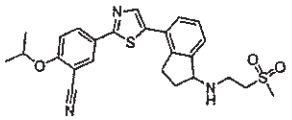
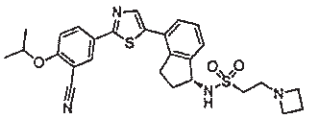
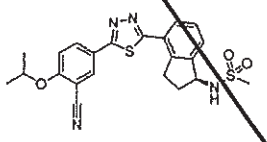
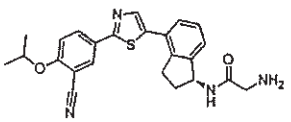
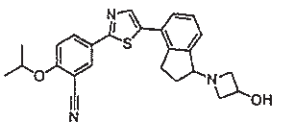
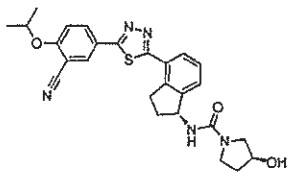
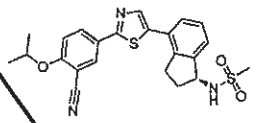
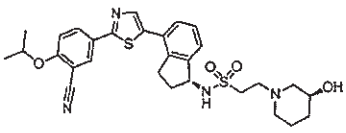
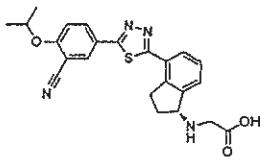
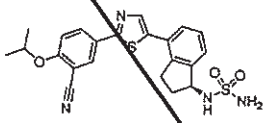
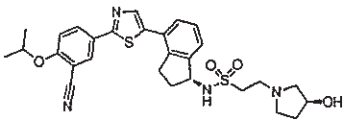
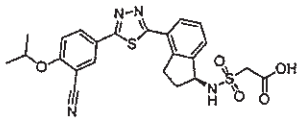
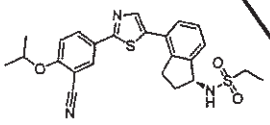
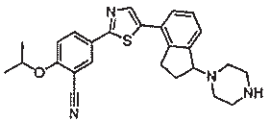
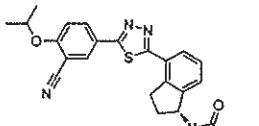
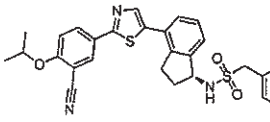
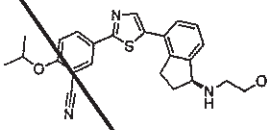
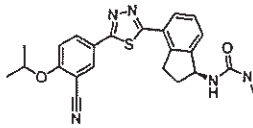
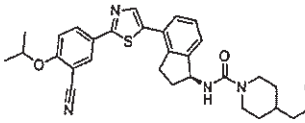
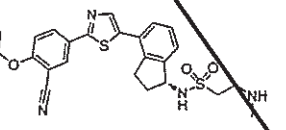
30. The compound of claims 1-27 wherein Y is CN.
31. The compound of claims 1-30 wherein X is –NR′R″.
32. The compound of claims 1-30 wherein X is –OR‴.
33. The compound of claim 32 wherein X is –OH.
34. The compound of claim 32 wherein X is –OCO-R^3.
35. The compound of claim 34 wherein R^3 is C_{1-3} alkyl.
36. The compound of claim 31 wherein R′ is H.
37. The compound of claim 31 wherein R′ is -COR^3.
38. The compound of claim 31 wherein R′ is -SO_2-R^3.
39. The compound of claim 31 wherein R″ is H.
40. The compound of claim 31 wherein R″ is -SO_2-R^5.
41. The compound of claim 31 wherein R″ is C_{1-4} alkyl optionally substituted with 1 or more R^4.
42. The compound of claim 31 wherein R″ is –$(CR^aR^b)_n$-R^4 ; 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.
43. The compound of claim 42 wherein n is 2.
44. The compound of claim 43 wherein R^4 is –OH, -NH_2, -NHR^3, -$N(R^7R^7)$, or –COOH.
45. The compound of claim 40 wherein R^5 is C_{1-4} alkyl optionally substituted with 1 or more R^4.
46. The compound of claim 40 wherein Y is CN.
47. The compound of claim 45 wherein R^5 is –C_2H_5-$N((R^7R^7)$ or –CH_2-CO-$N(R^7R^7)$.
48. The compound of claim 46 wherein R^5 is C_2H_5–O-R^3.
49. The compound of claim 32 wherein X is –NH-CO-$N(R^7R^7)$.
50. The compound of claims 1 and 20-27 wherein the compound is selected from **compounds 1-227:**

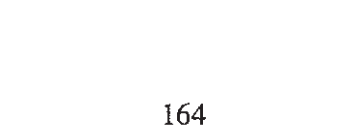




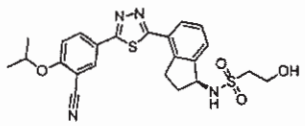
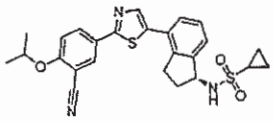
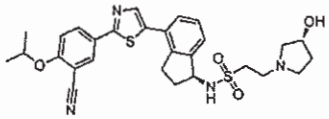
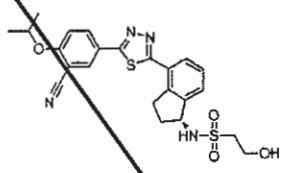
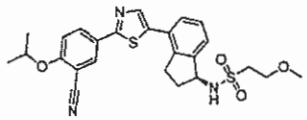
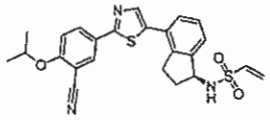
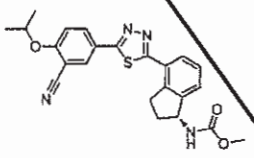
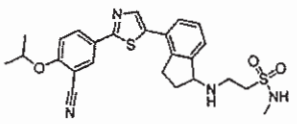
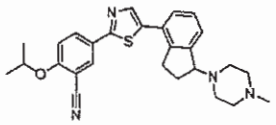
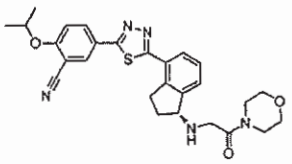
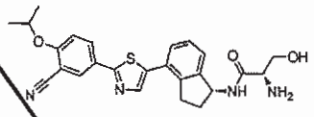
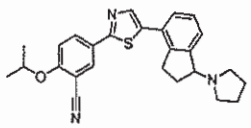
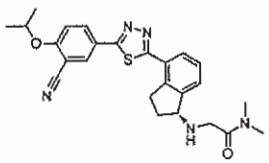
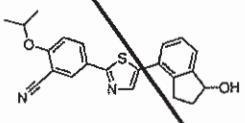
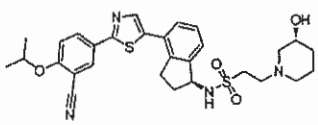
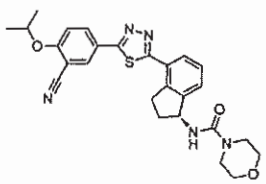
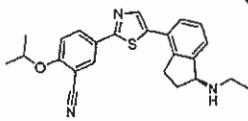
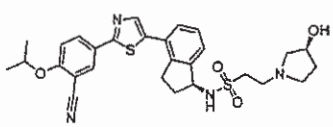
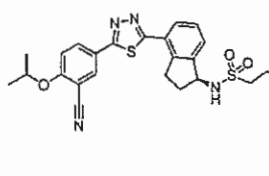
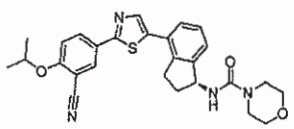
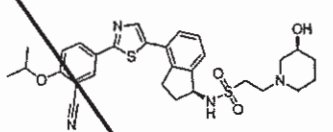
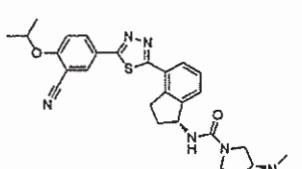
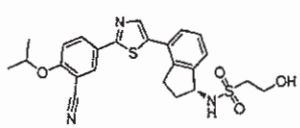
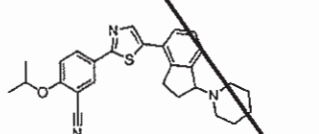
















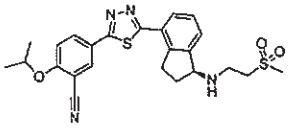
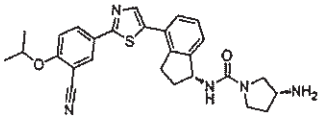
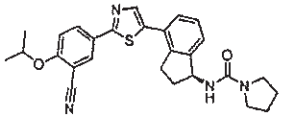
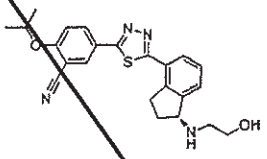
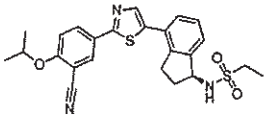
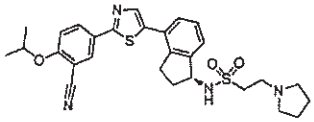
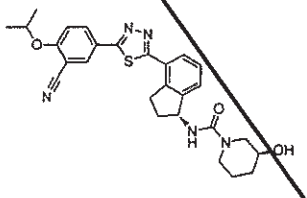
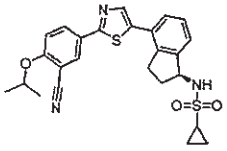
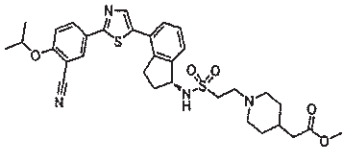
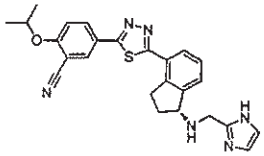
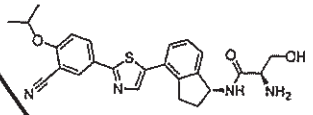
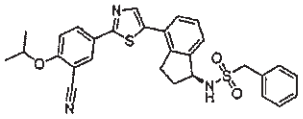
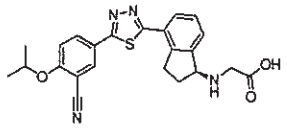
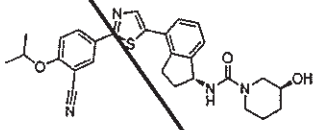
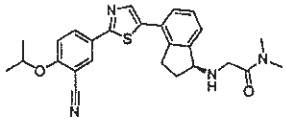
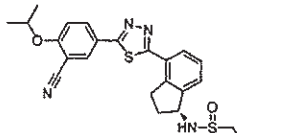
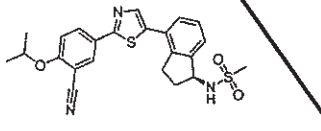
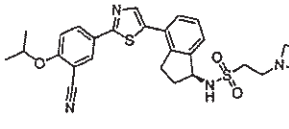
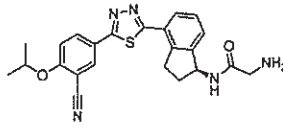
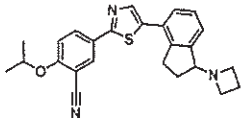
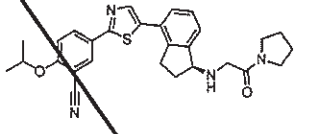
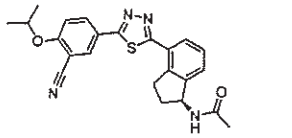
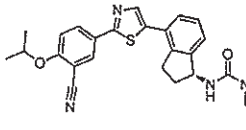
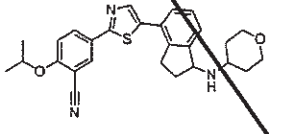


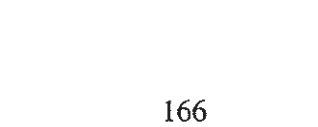

























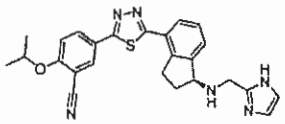
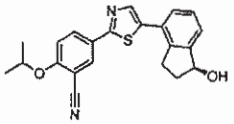
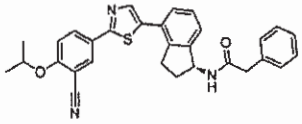
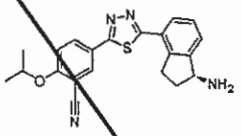
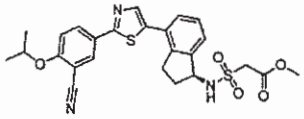
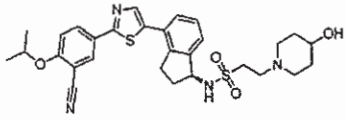
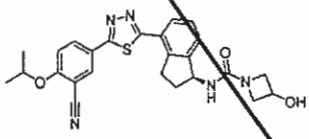
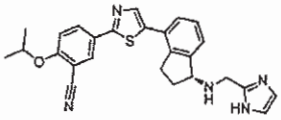
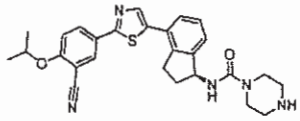
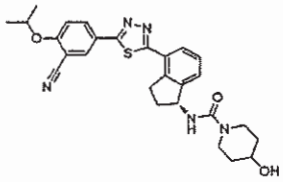
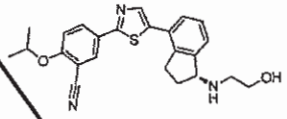
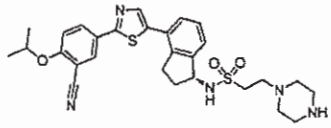
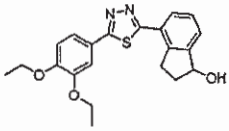
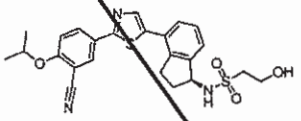
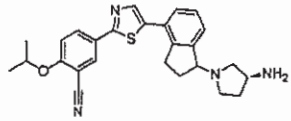
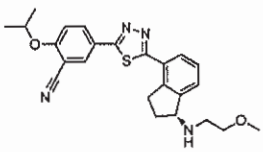
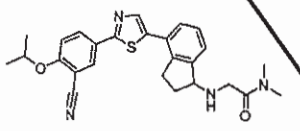
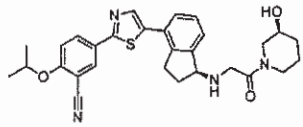
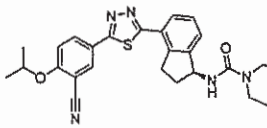
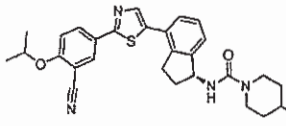
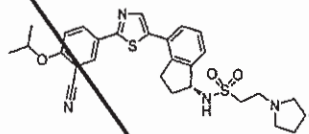
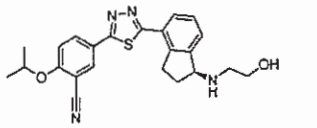
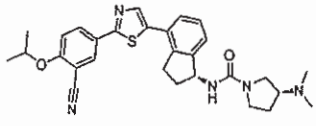
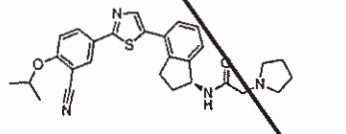

























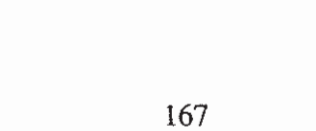


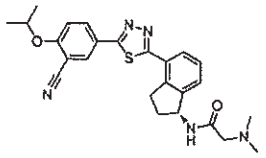
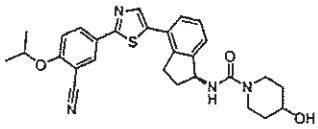
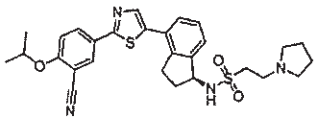
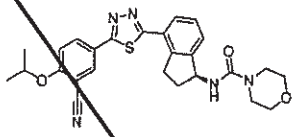
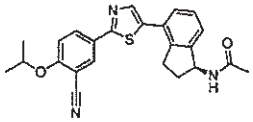
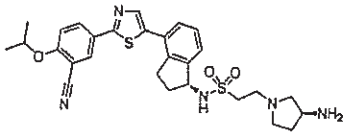
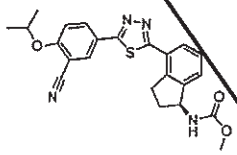
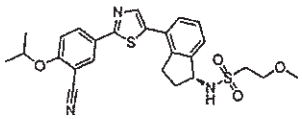
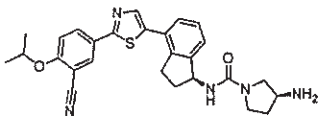
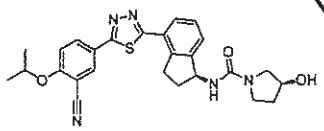
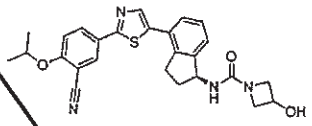
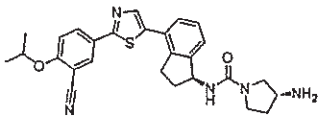
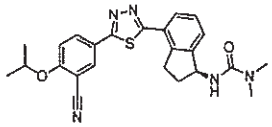
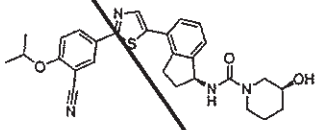
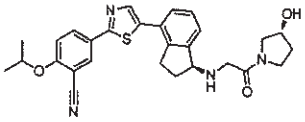
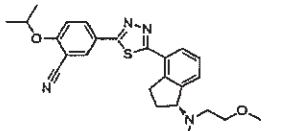
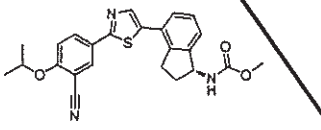
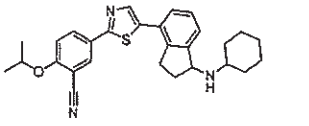
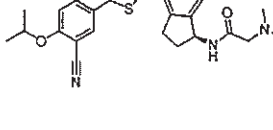
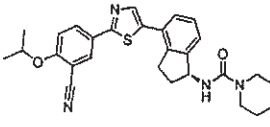
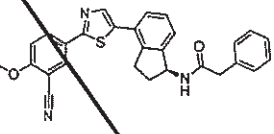
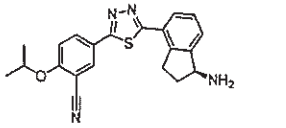
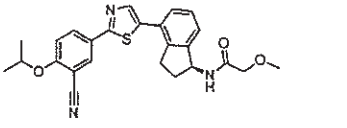
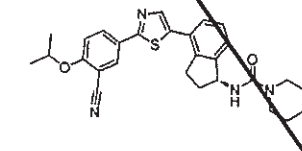

























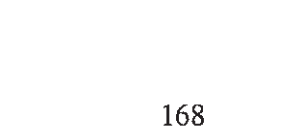

























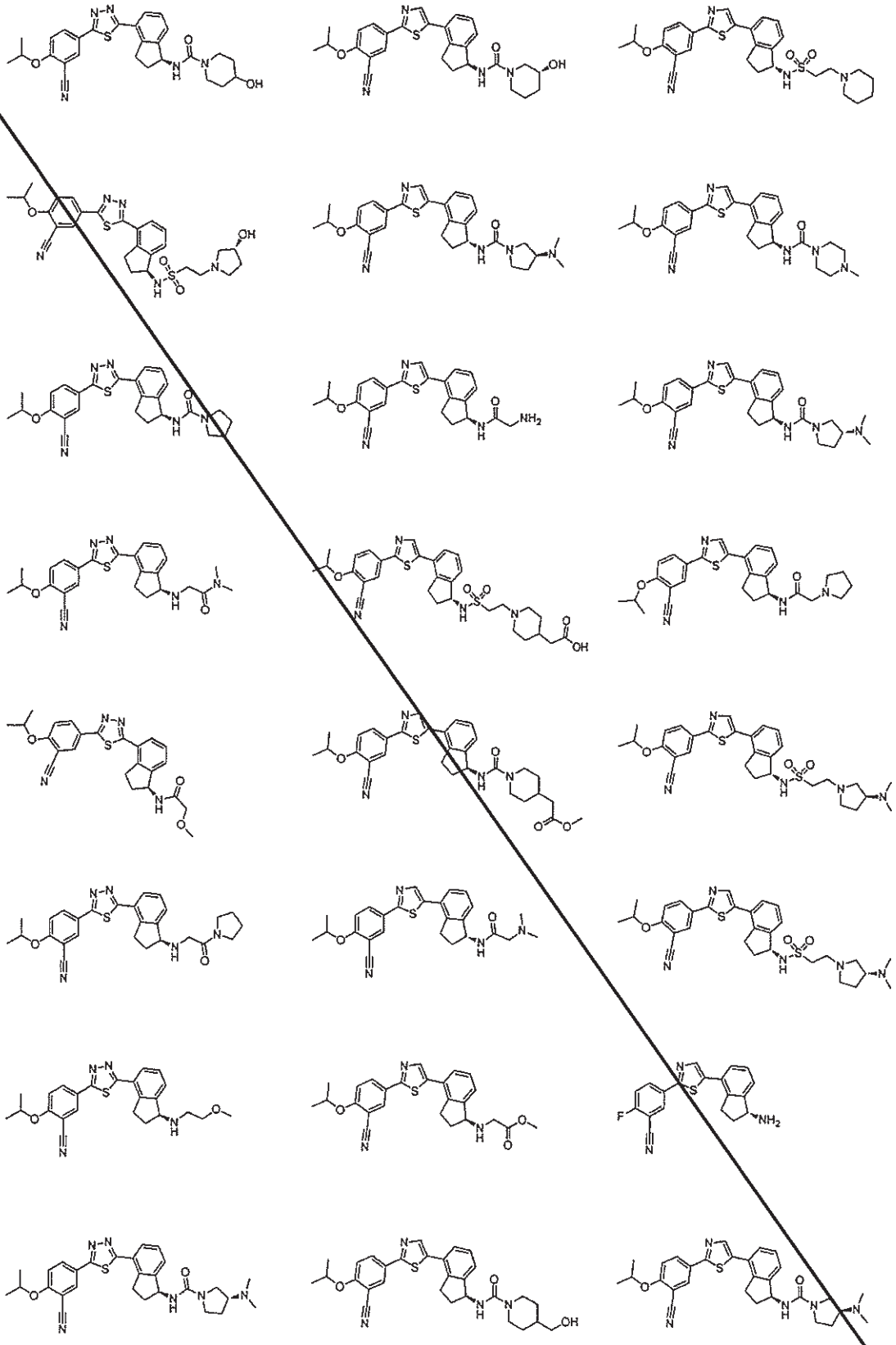


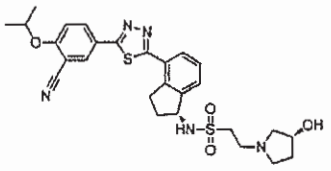
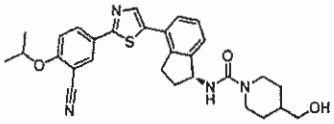
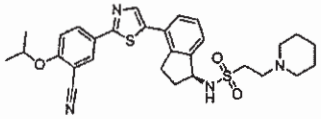
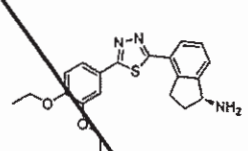
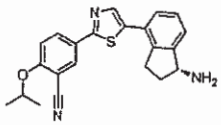
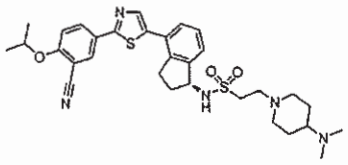
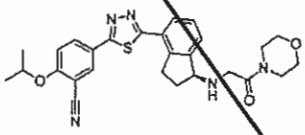
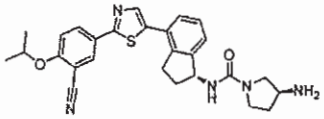
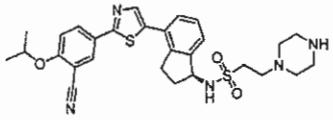
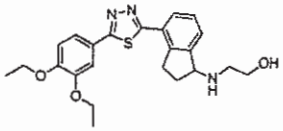
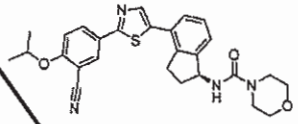
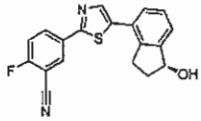
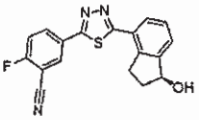
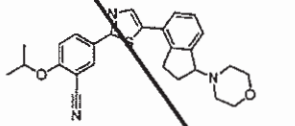
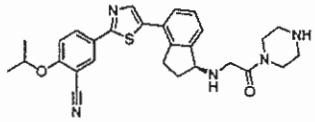
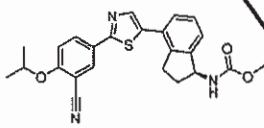
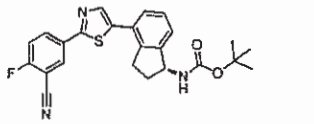
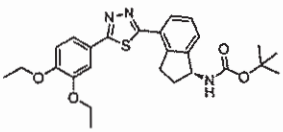
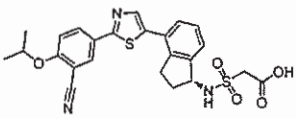
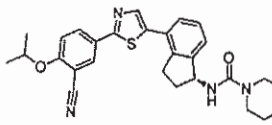
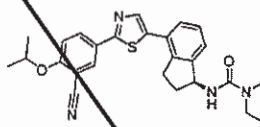
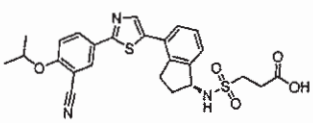
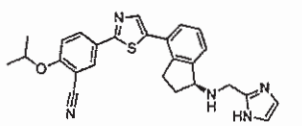
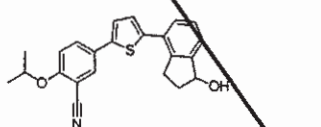

























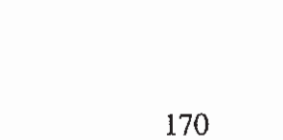


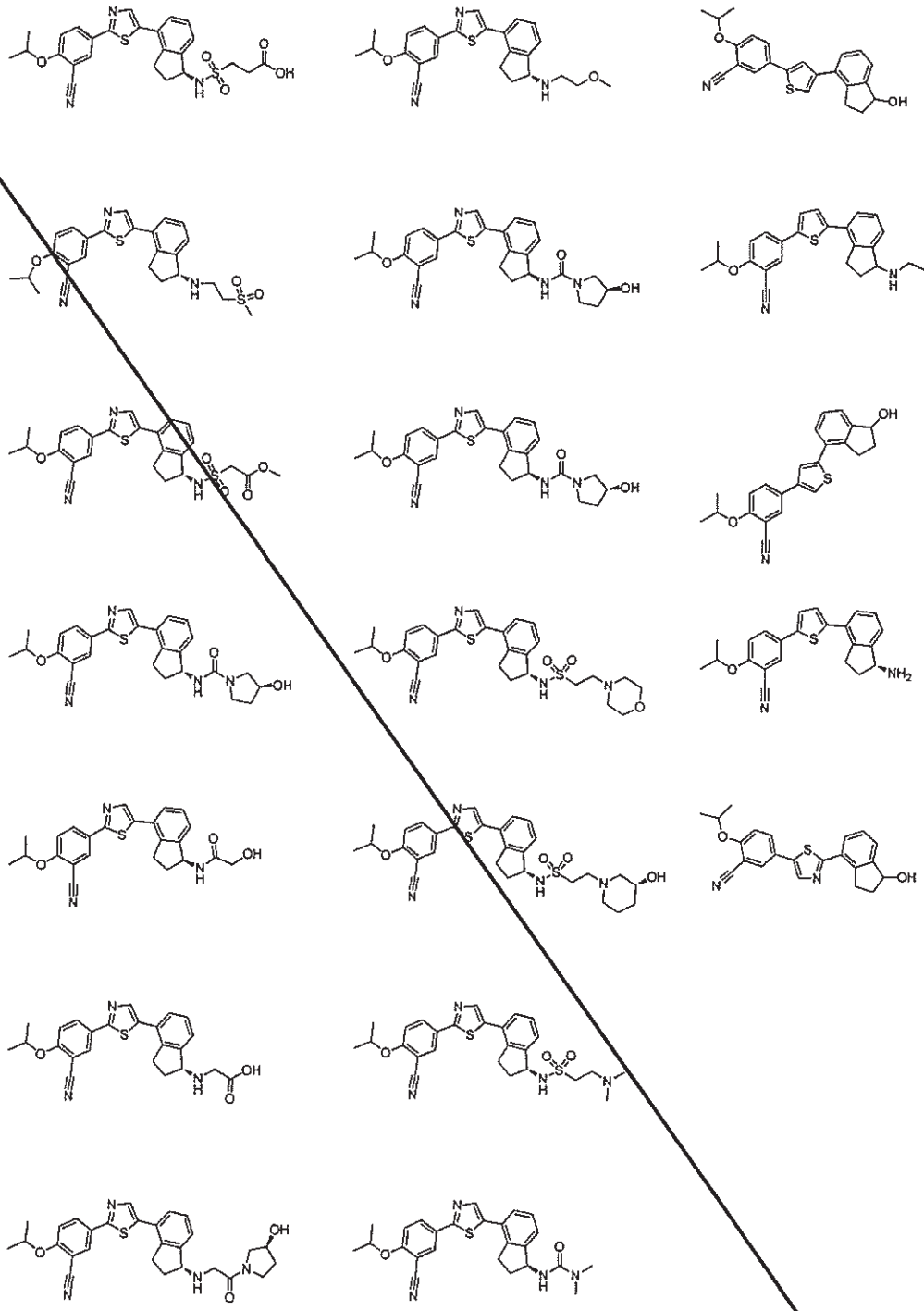





























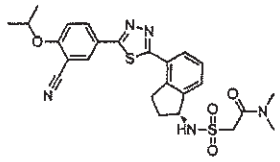
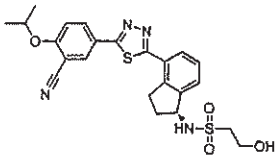
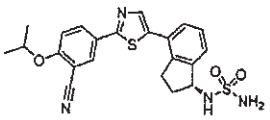





























or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof.

51. The compound of claim 50 wherein the compound is selected from compounds 43, 46, and 166:

or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof.

52. A pharmaceutical composition comprising a compound of claims 1-51 and a suitable excipient.
53. A pharmaceutical composition comprising the compound of claims 1-51 and a second medicament.
54. The composition of claim 53 wherein the second medicament is medically indicated for the treatment of multiple sclerosis, transplant rejection, or acute respiratory distress syndrome.
55. The use of a compound of any one of claims 1-51 for preparation of a medicament.
56. 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 1-51 or the composition of claims 52-53.
57. The method of claim 56 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.
58. The method of claim 56 wherein the sphingosine-1-phosphate receptor subtype 1 is disposed within a living mammal.
59. 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 1-51 to the patient at a frequency and for a duration of time sufficient to provide a beneficial effect to the patient.
60. The method of claim 59 wherein selective activation or agonism of an S1P subtype 1 receptor with respect to other subtypes of S1P receptor is medically indicated.

61. The method of claim 59 or 60 wherein the malcondition comprises multiple sclerosis, transplant rejection, acute respiratory distress syndrome, ulcerative colitis, influenza, Crohn's disease or adult respiratory distress syndrome.

62. 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, and wherein a carbon of the phenyl ring is halo substituted;

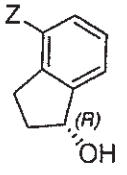
(ii) reacting such compound with a chiral reagent selected from the group consisting of a Corey Bakshita Shibata-oxazaborolidine and a chiral sulfinamide of the form $RS(=O)NH_2$ where R is selected from the group consisting of t-butyl, branched C_{2-6} alkyl and C_{3-8} cycloalkyl; and

(iii) forming the 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.

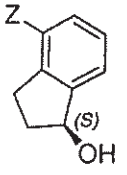
63. The method of claim 62 wherein the chiral reagent is the Corey Bakshita Shibata-oxazaborolidine.

64. The method of claims 62-63 wherein the chiral reagent is (*R*)-(-)-(2)-methyl-CBS-oxazaborolidine or (*S*)-(-)-(2)-methyl-CBS-oxazaborolidine.

65. The method of claims 63-64 wherein the compound comprising an indane moiety provided in step (i) is contacted with the chiral reagent to form in step (iii) Formula **VI-R** or **VI-S**:



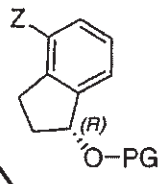
VI-R



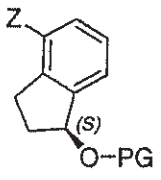
VI-S

wherein Z is Cl, Br or I.

66. The method of claim 65 wherein the method further comprises the step of protecting the hydroxy group of Formula **VI-R** or **VI-S** by treating Formula **VI-R** or **VI-S** with a protecting agent to form Formula **VIa-R** or **VIa-S**:



VIa-R

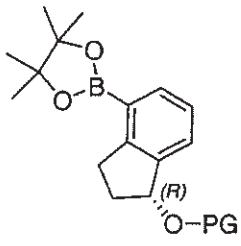


VIa-S

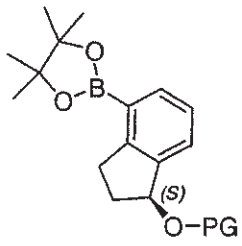
wherein PG is a protecting group.

67. The method of claim 66 wherein the protecting agent is TBSCl.

68. The method of claims 66-67 wherein the method further comprises the step of reacting Formula **VIa-R** or **VIa-S** with boronic acid or bis(pinacolato)diboron to form a boronic acid or boronate ester of Formula **VIb-R** or **VIb-S**:



VIb-R

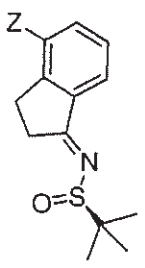


VIb-S.

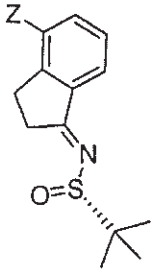
69. The method of claim 62 wherein the chiral reagent is $RS(=O)NH_2$ and the compound comprising an indane moiety is enantiomerically enriched with respect to a carbon-nitrogen bond on a ring carbon of the five-membered ring of the indane moiety.

70. The method of claim 69 wherein the chiral reagent is t-Bu-$S(=O)NH_2$.

71. The method of claims 69-70 wherein the compound comprising an indane moiety provided in step (i) is contacted with the chiral reagent to form in step (ii) Formula **VII**:



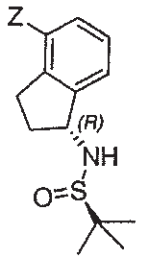
VII -R



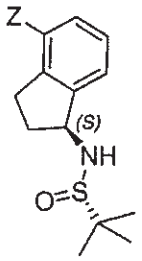
VII-S

wherein Z is Cl, Br or I.

72. The method of claims 69-71 wherein a compound of Formula **VIII-R** or **VIII-S** is formed in step (iii):

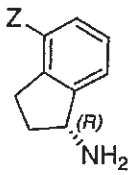


VIII-R

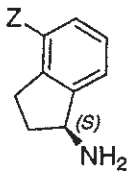


VIII-S.

73. The method of claim 72 wherein the method further comprises the step of contacting Formula **VIII-R** or **VIII-S** with 1,4-dioxane in the presence of an acid to form Formula **VIb-R** or **VIb-S** or Formula **IX-R** or **IX-S**:

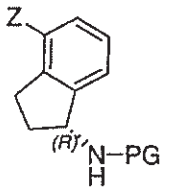


IX –R

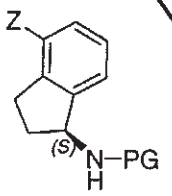


IX -S.

74. The method of claims 73 wherein the method further comprises the step of protecting the amino group by treating Formula **IX-R** or **IX-S** with a protecting agent to form Formula **IXa-R** or **IXa-S**:



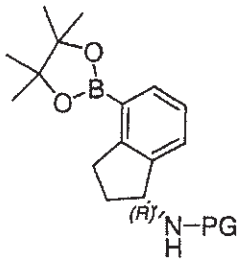
IXa-R



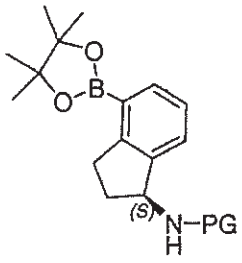
IXa -S.

75. The method of claims 74 wherein the protecting agent is di-*tert*-butyldicarbonate.

76. The method of claims 74-75 wherein the method further comprises the step of reacting Formula **IXa-R** or **IXa-S** with boronic acid or bis(pinacolato)diboron to form a boronic acid or boronate ester of Formula **IXb-R** or **IXb-S**:

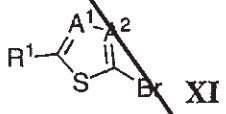


IXb –R



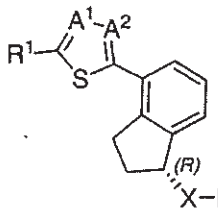
IXb -S.

77. The method of claims 68 or 76 wherein the method further comprises the step of reacting Formula **VIb-R**, Formula **VIb-S**, Formula **IXb-R** or Formula **IXb-S** with Formula **XI** to form Formula **XII-R** or **XII-S**:

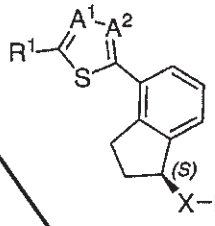


XI

to form Formula **XII-R** or **XII-S:**



XII-R

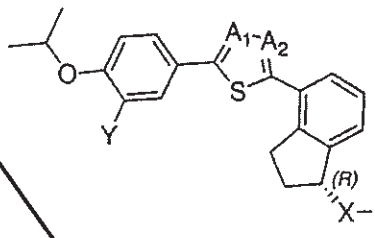


XII-S

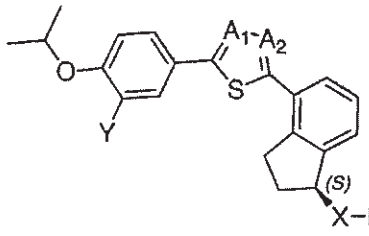
wherein each A^1 and each A^2 is independently N, or CH; R^1 is di-substituted phenyl or di-substituted pyridinyl where the phenyl and pyridinyl substituents are each independently selected from the group consisting of halo, nitro, cyano, perfluromethyl, fluorinated methyl, and C_{1-4}-alkoxy; provided that if R^1 is di-substituted phenyl, such phenyl is para-substituted with C_{1-4}-alkoxy; and X is NH or O.

78. The method of claim 77 wherein R^1 is di-substituted phenyl where the phenyl substituents are F and Y, wherein Y is –CN, -Cl, I, -O-R^3, -COOH, -$COOR^3$, or -CF_3.

79. The method of claims 78 wherein the method further comprises the step of reacting Formula **XII-R** or **XII-S** with *i*PrOH in the presence of NaO*i*Pr to from Formula **XIII-R** or **XIII-S**:



XIII-R



XIII-S.

80. The method of claims 79 wherein the method further comprises the step of deprotecting the hydroxyl group wherein X is O, or the amino group wherein X is NH, by treating Formula **XIII-R** or **XIII-S** with a deprotecting agent.

81. The method of claims 80 wherein the method further comprises the step of converting the deprotected amino group to a secondary amine.

82. The method of claims 78-81 wherein Y is CN.

83. The method of claims 77-82 wherein A^1 is N and A^2 is N.

84. The method of claim 83 wherein Formula **XI** is prepared following the process comprising the step of

a) treating a di-substituted benzaldehyde with potassium phosphate monobasic to form a di-substituted benzoic acid;

b) contacting the di-substituted benzoic acid with $H_2NNHCSNH_2$ to form an amino-1,3-4-thiadizole having a di-substituted phenyl group substituted on the thiadiazole moiety; and

c) treating the amino-1,3-4-thiadizole in step b) with a mixture of copper bromide and isoamylnitrite.

85. The method of claims 77-82 wherein A^1 is N and A^2 is CH.

86. The method of claim 85 wherein Formula **XI** is prepared following the process comprising the step of

a) contacting 2-bromothiazole with a (di-substituted phenyl)boronic acid to form a 2-(di-substituted phenyl)thiazole; and

b) treating the 2-(di-substituted phenyl)thiazole with NBS.

87. The method of claims 77-82 wherein A^1 is CH and A^2 is N.

88. The method of claim 88 wherein Formula **XI** is prepared following the process comprising the step of

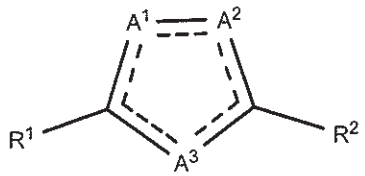
a) contacting 5-(tributylstannyl)thiazole with an iodobenzene having two other substituents to form a 5-(di-substituted phenyl)thiazole; and

b) treating the 2-(di-substituted phenyl)thiazole with NBS.

89. The method of claims 62-88 wherein a compound of claims 1- 51 is prepared.

We claim:

1. A compound of Formula (**I**) or a pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof:



(I)

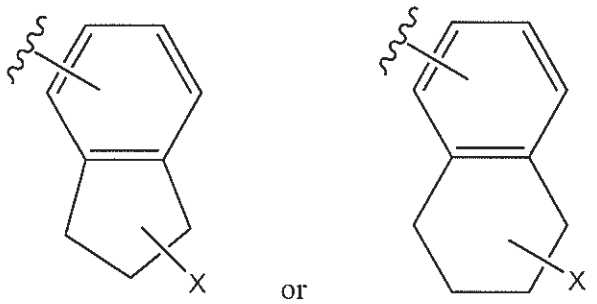
wherein

a dashed line signifies that a single bond or a double bond can be present, provided that there are two double bonds and three single bonds in the ring comprising A^1, A^2, and A^3;

A^1, A^2, and A^3 each independently is CH or S or N; provided that one of A^1, A^2, and A^3 is S;

R^1 is di-substituted phenyl or di-substituted pyridinyl where the phenyl and pyridinyl substituents are each independently selected from the group consisting of halo, nitro, cyano, perfluromethyl, fluorinated methyl, and C_{1-4}-alkoxy; provided that if R^1 is di-substituted phenyl, such phenyl is para-substituted with C_{1-4}-alkoxy;

R^2 is



wherein a wavy line indicates a point of attachment;

X is –NR′R″ or -OR‴;

R′ is H, C_{1-4} alkyl, n-hydroxy C_{1-4} alkyl, $-SO_2-R^3$, or $-CO-R^3$;

R″ is H, $-SO_2-R^5$, C_{1-4} alkyl optionally substituted with 1 or more R^4, or a ring moiety optionally substituted with R^6 wherein such ring moiety is piperidinyl, cyclohexyl, morpholinyl, thiazolyl, pyrazolyl, pyrrolidinyl, imidazolyl, or phenyl;

R‴ is H, C_{1-4} alkyl, or $-CO-R^3$

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, $-(CH_2)_m$-$COOR^3$, $-N(R^3R^3)$, and $-(CH_2)_m$-$CO-N(R^7R^7)$;

each R^3 is independently C_{1-4} alkyl or H;

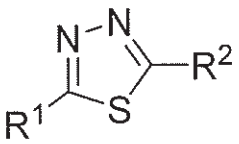
each R^4 is independently H, halo, OH, oxo, =NH, NH_2, -COOH, F, $-NHR^3$, $-N(R^7R^7)$,$–SO_2-R^3$, $–SO_2-N(R^7R^7)$, $-N(R^3)–SO_2-R^3$, $-COOR^3$, $-OCO-R^3$, $-CO-N(R^7R^7)$, $-N(R^3)-COR^3$, C_{1-3} alkyl, C_{1-3} alkoxy, and a ring moiety optionally substituted with R^6 wherein such ring moiety is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, pyrazolyl, imidazolyl, benzimidazolyl, azetidinyl, cyclobutinyl, or phenyl;

each R^5 is independently R^4, C_{1-4} alkyl, C_{3-6} cycloalkyl, or C_{1-4} alkyl optionally substituted with 1 or more R^4;

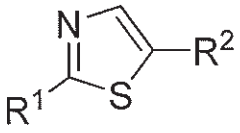
each R^6 is independently halo, OH, $-NH_2$, $-NHR^3$, $-N(R^3R^3)$, -COOH, $-COOR^3$, $-NHCO-R^3$; each R^7 is independently C_{1-4} alkyl or H, or two R^7 taken together with the nitrogen atom to which they are bound form a 4, 5, or 6 membered saturated heterocyclic ring containing 0 or 1 additional heteroatoms where such additional heteroatom is O or N wherein such heterocycle is optionally substituted with –OH, $-NH_2$, $-N(R^3R^3)$, n-hydroxy C_{1-4} alkyl, $-(CH_2)_m$-COOH, or $-(CH_2)_m$-$COOR^3$;

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

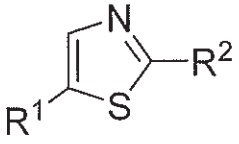
2. The compound of claim 1 wherein the structure of Formula **I** is selected from the group consisting of formulas **a-i** through **a-x**:



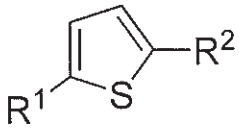
a-i



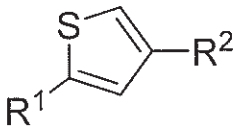
a-ii



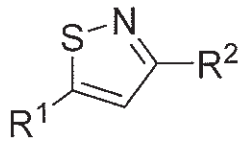
a-iii



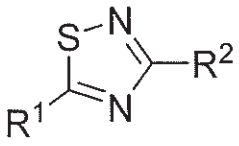
a-iv



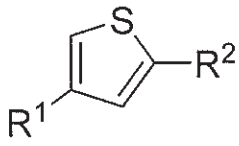
a-v



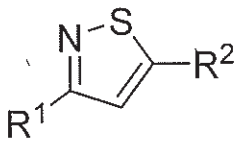
a-vi



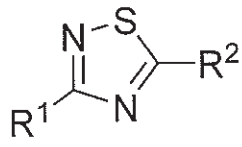
a-vii



a-viii



a-ix



a-x

3. The compound of claim 1 wherein A^1 is S.

4. The compound of claim 1 wherein A^2 is S.

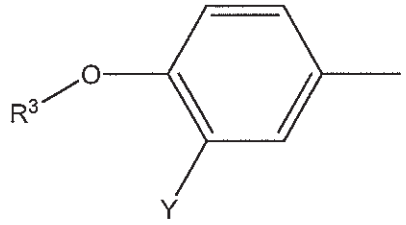
5. The compound of claim 1 wherein A^3 is S.

6. The compound of claim 5 wherein A^1 is N and A^2 is CH or N.

7. The compound of claim 6 wherein A^2 is CH.

8. The compound of claim 6 wherein A^2 is N.

9. The compound of claim 1 wherein R^1 is



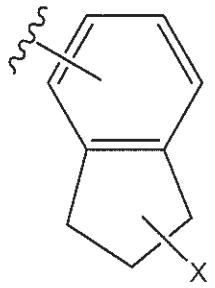
;

R^3 is C_{2-4} alkyl; and Y is –CN, -Cl, -O-R^3, or -CF_3.

10. The compound of claim 9 wherein R^3 is isopropyl or ethyl.

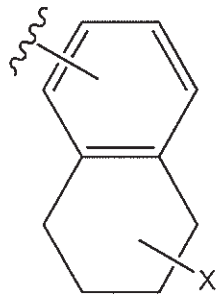
11. The compound of claim 9 wherein Y is -CN or –O-C_2H_5.

12. The compound of claim 1 wherein R^2 is



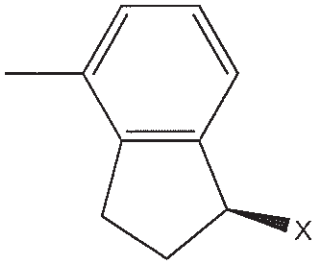
.

13. The compound of claim 1 wherein R^2 is

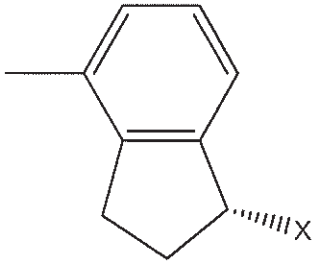


.

14. The compound of claim 12 wherein R^2 is

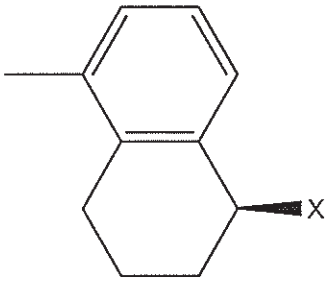


or

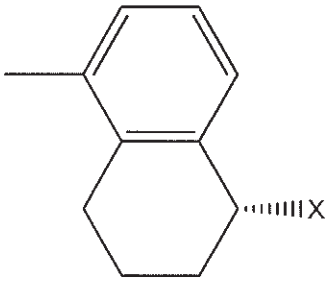


.

15. The compound of claim 13 wherein R^2 is

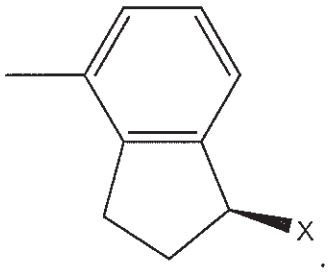


or



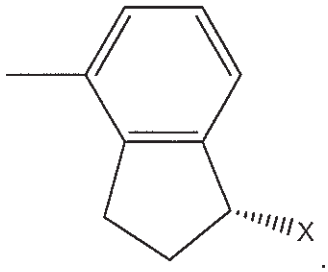
.

16. The compound of claim 14 wherein R^2 is



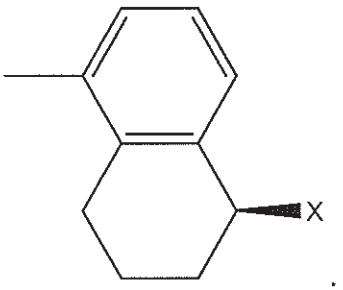
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17. The compound of claim 14 wherein R^2 is

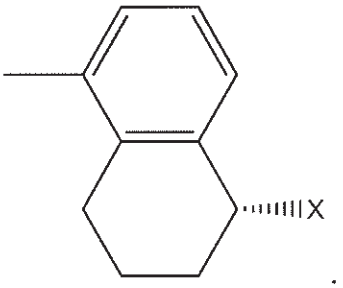


.

18. The compound of claim 15 wherein R^2 is



19. The compound of claim 15 wherein R^2 is



20. The compound of claim 14 wherein the compound is substantially enantiomerically pure.

21. The compound of claim 1 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.

22. The compound of claim 21 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.

23. The compound of claim 1 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.

24. The compound of claim 23 wherein the therapeutic index is at least 10.

25. The compound of claim 23 wherein the therapeutic index is at least 20.

26. The compound of claim 23 wherein the therapeutic index for the compound is greater than the therapeutic index for the enantiomer of the compound.

27. The compound of claim 26 wherein the therapeutic index for the compound is at least 150% of the therapeutic index for the enantiomer of the compound.

28. The compound of claim 9 wherein Y is Cl.

29. The compound of claim 9wherein Y is CF_3.

30. The compound of claim 9 wherein Y is CN.

31. The compound of claim 1 wherein X is -NR′R″.

32. The compound of claim 1 wherein X is -OR‴.

33. The compound of claim 32 wherein X is –OH.

34. The compound of claim 32 wherein X is –OCO-R^3.

35. The compound of claim 34 wherein R^3 is C_{1-3} alkyl.

36. The compound of claim 31 wherein R′ is H.

37. The compound of claim 31 wherein R′ is $-COR^3$.

38. The compound of claim 31 wherein R′ is $-SO_2-R^3$.

39. The compound of claim 31 wherein R″ is H.

40. The compound of claim 31 wherein R″ is $-SO_2-R^5$.

41. The compound of claim 31 wherein R″ is C_{1-4} alkyl optionally substituted with 1 or more R^4.

42. The compound of claim 31 wherein R″ is $-(CR^aR^b)_n-R^4$; 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.

43. The compound of claim 42 wherein n is 2.

44. The compound of claim 43 wherein R^4 is –OH, $-NH_2$, $-NHR^3$, $-N(R^7R^7)$, or –COOH.

45. The compound of claim 40 wherein R^5 is C_{1-4} alkyl optionally substituted with 1 or more R^4.

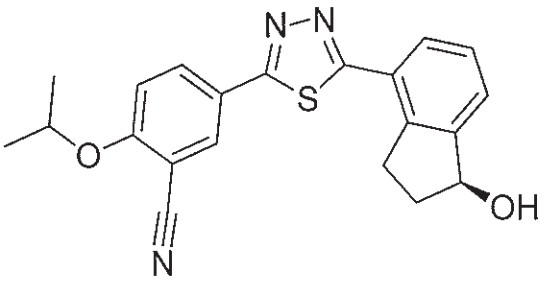
46. The compound of claim 9 wherein Y is CN.

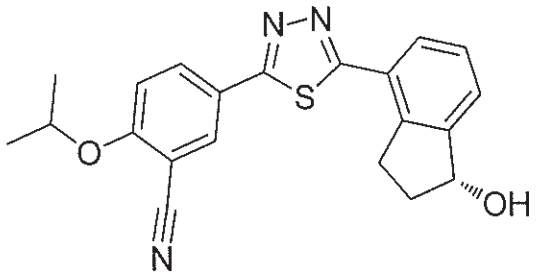
47. The compound of claim 45 wherein R^5 is $-C_2H_5-N(R^7R^7)$ or $-CH_2-CO-N(R^7R^7)$.

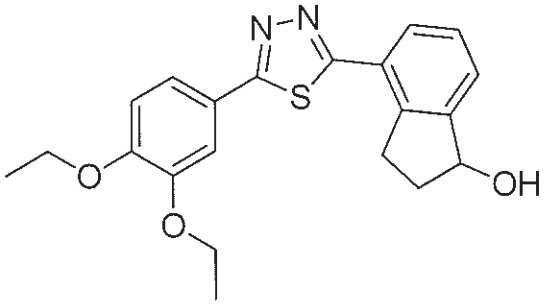
48. The compound of claim 46 wherein R^5 is $C_2H_5-O-R^3$.

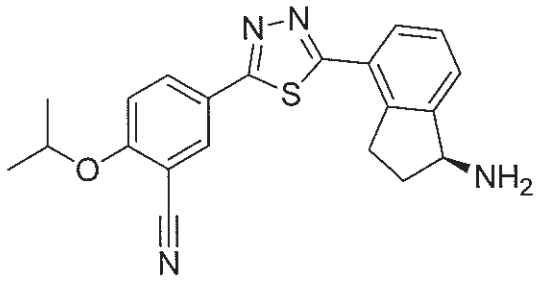
49. The compound of claim 31 wherein X is $-NH-CO-N(R^7R^7)$.

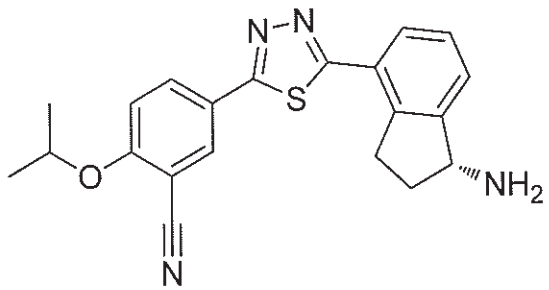
50. The compound of claim 1 wherein the compound is selected from:

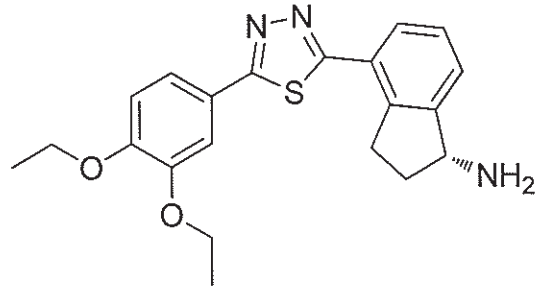


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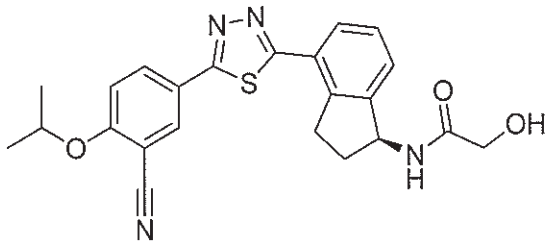
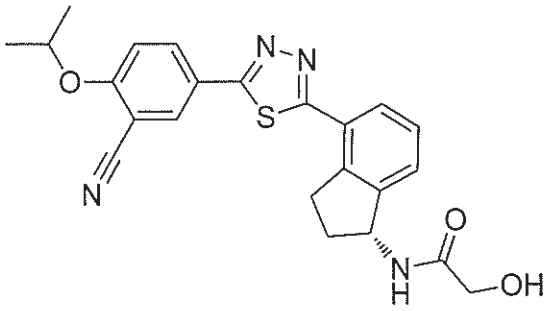
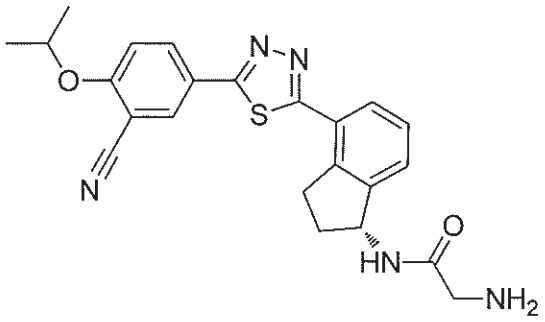
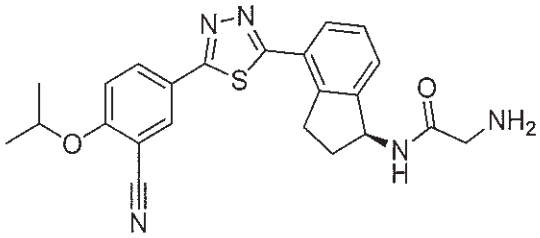
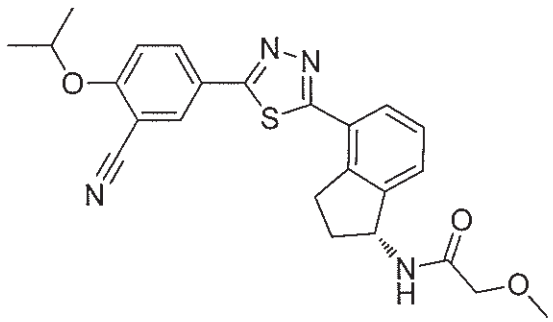
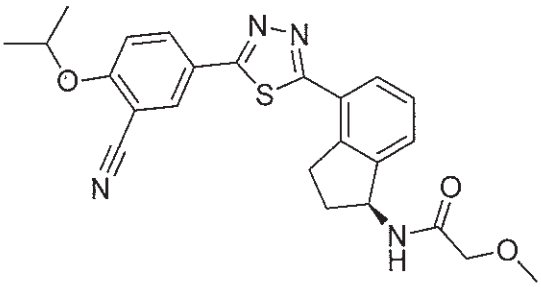
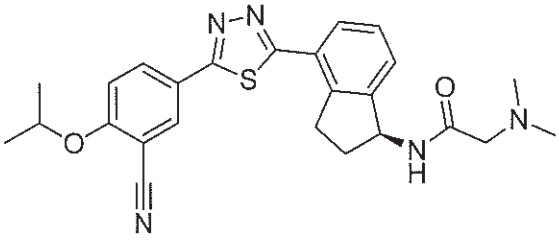
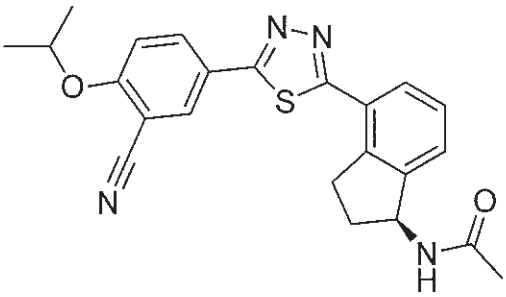
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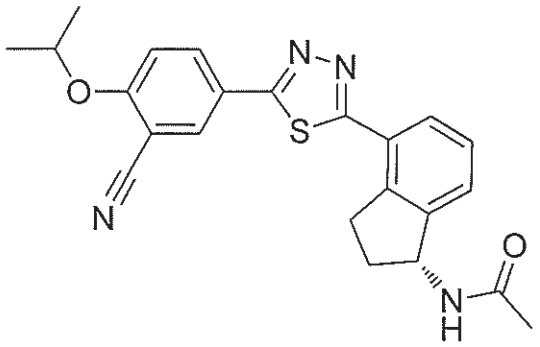
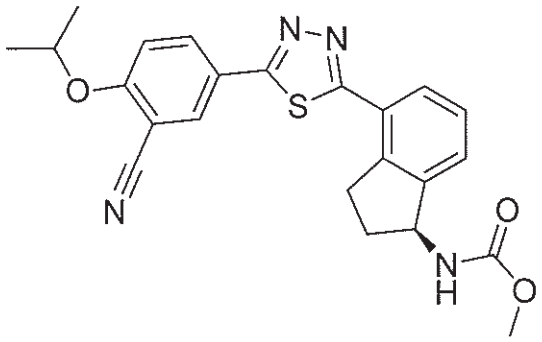
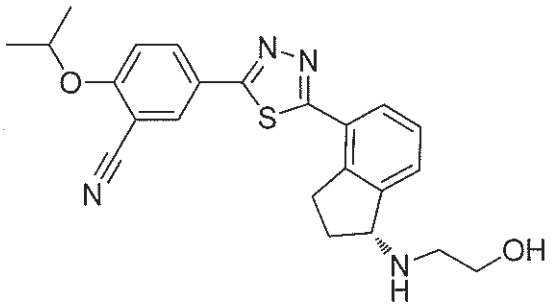
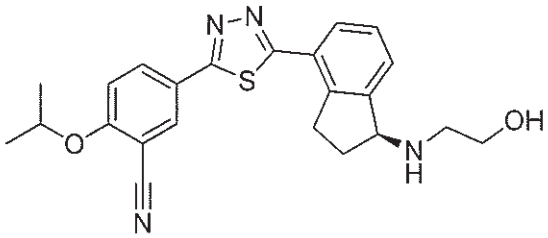
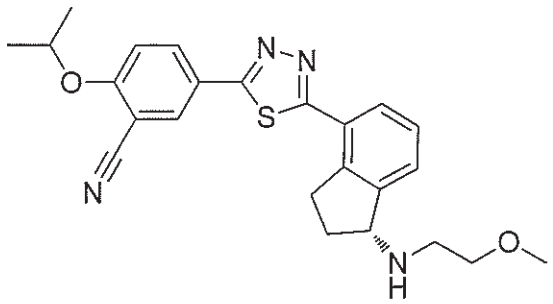
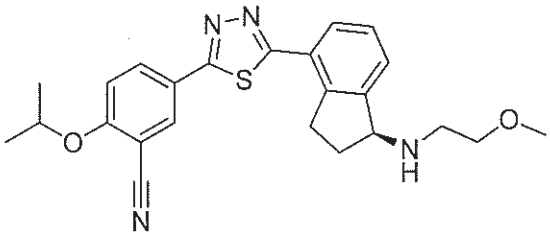
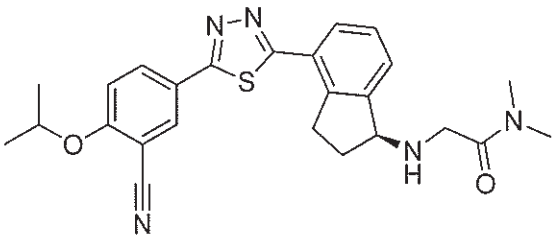
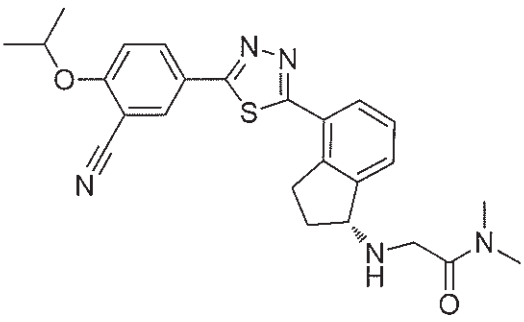
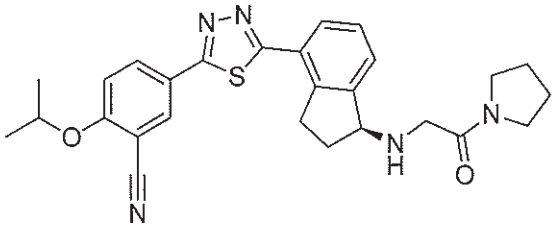
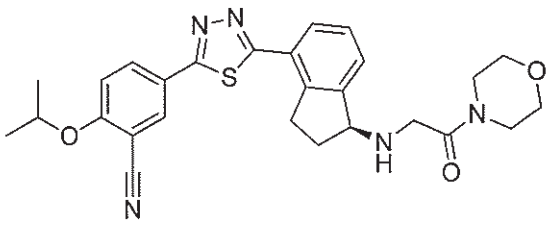
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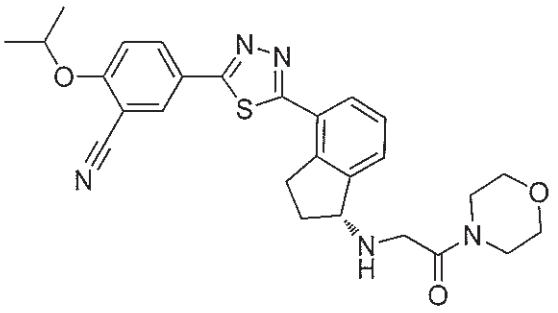
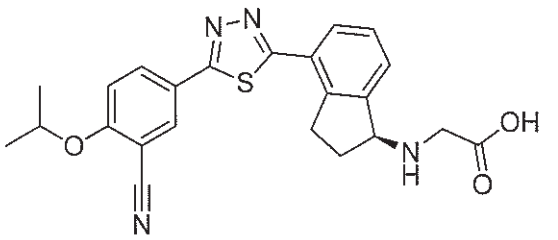
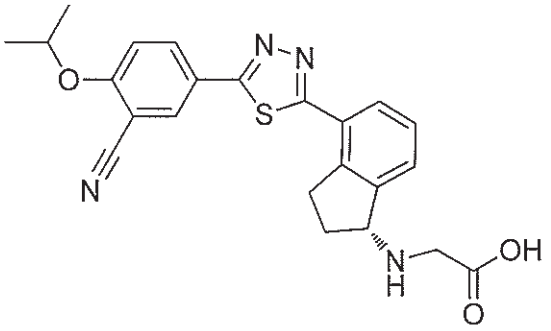
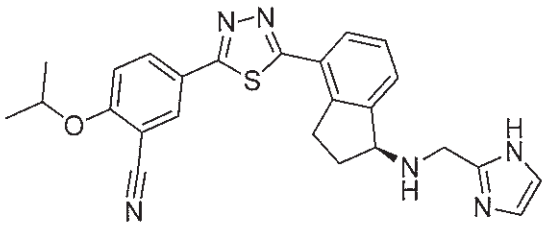
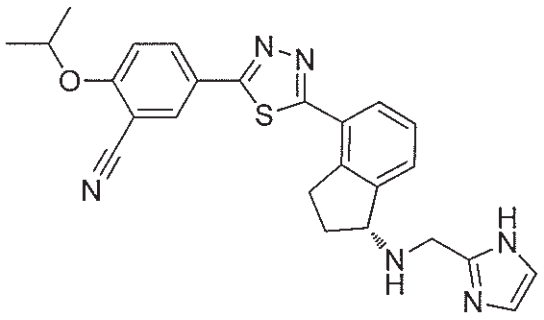
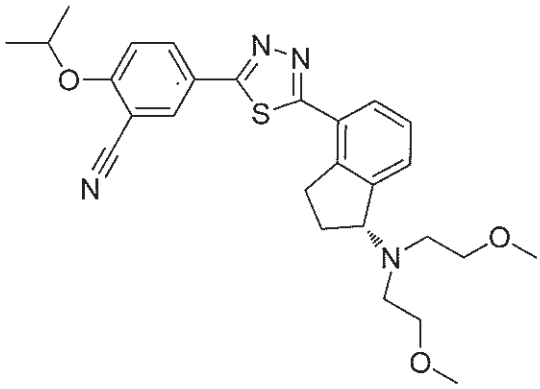
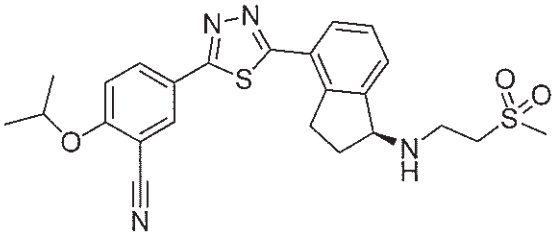
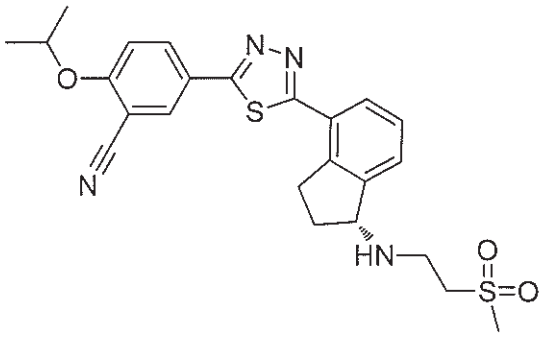
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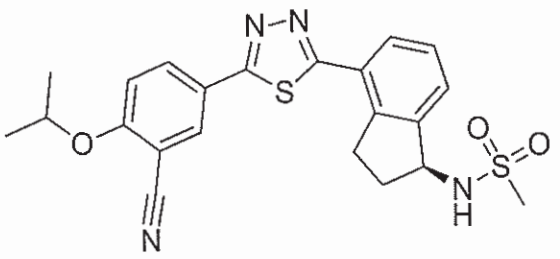
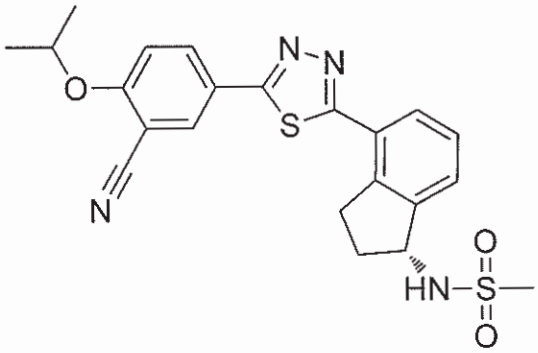
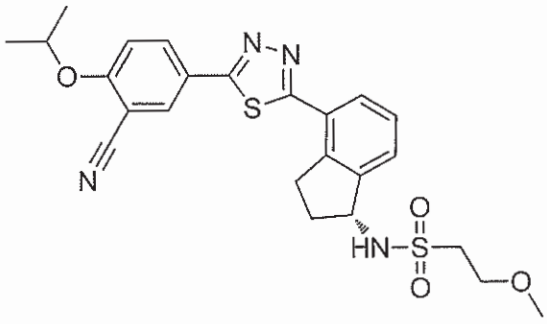
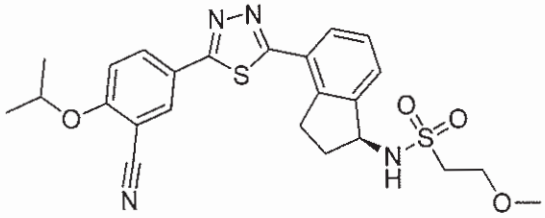
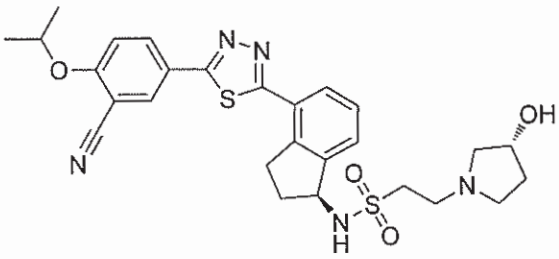
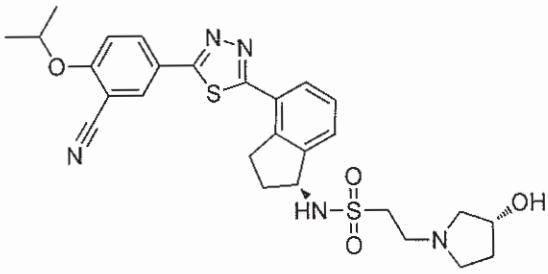
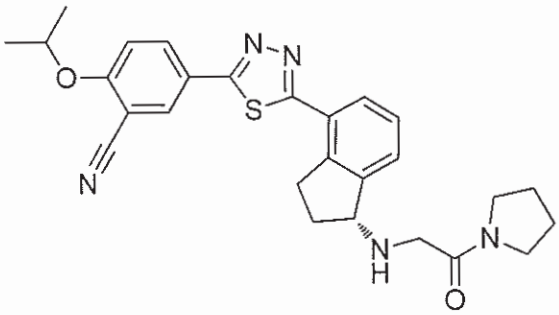
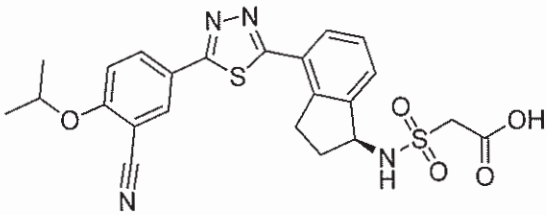
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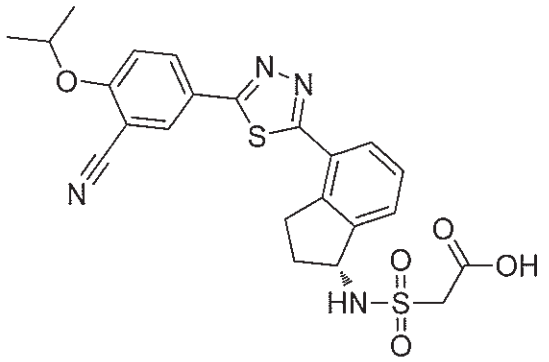
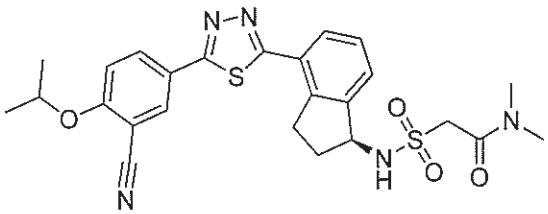
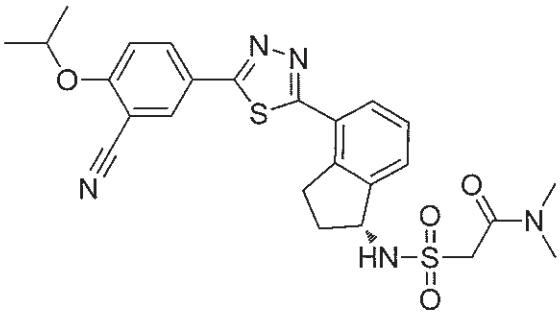
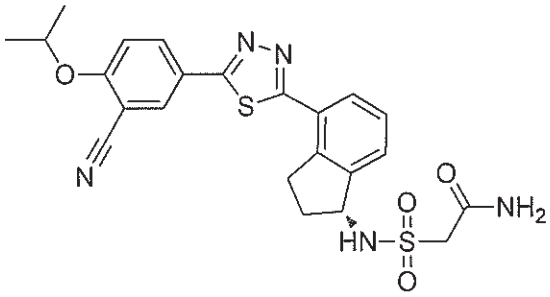
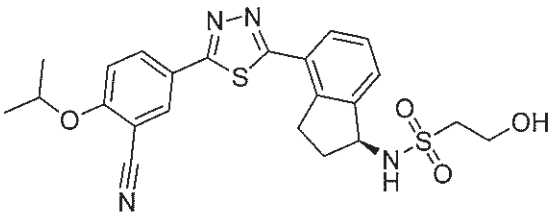
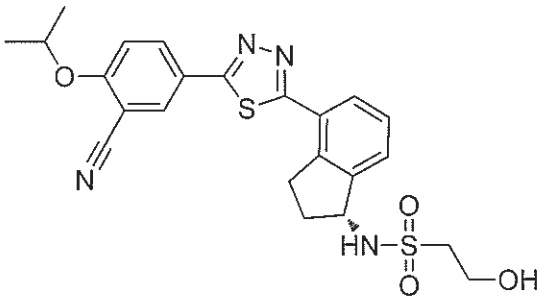
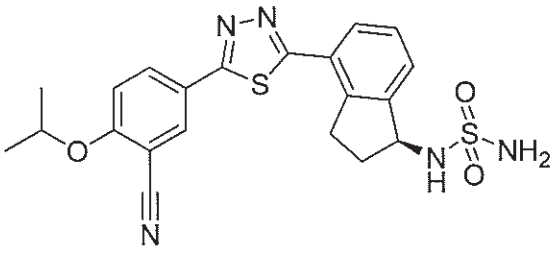
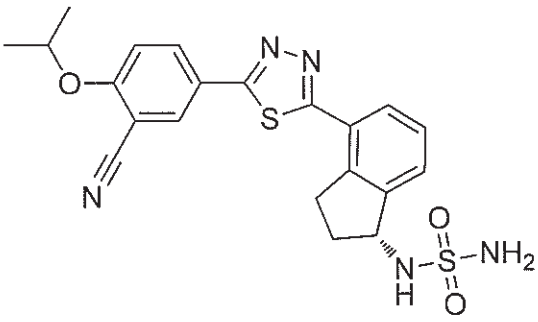
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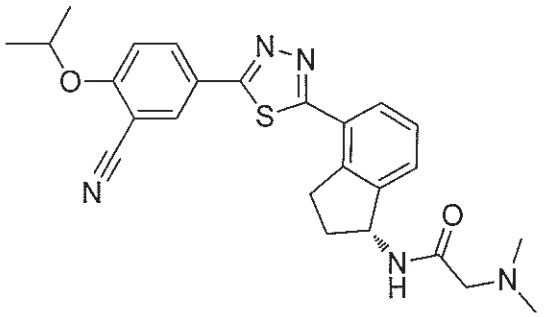
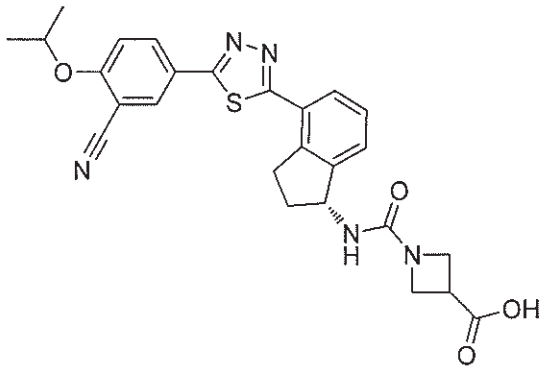
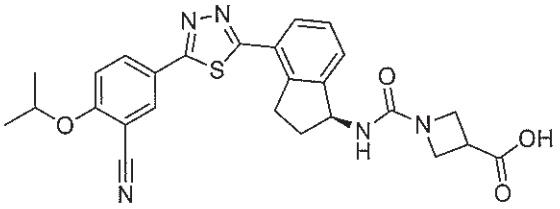
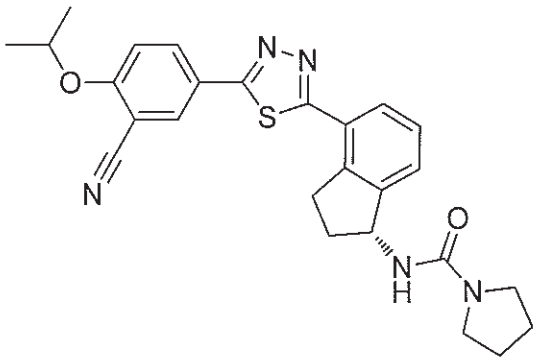
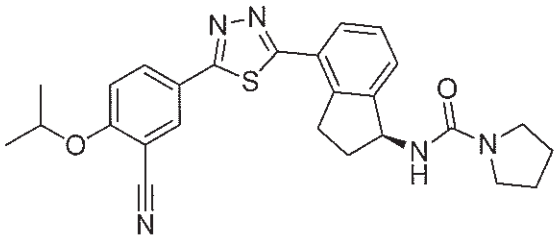
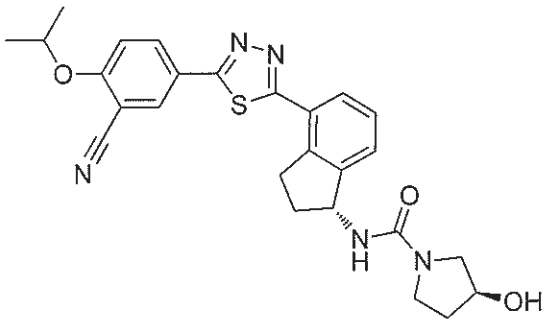
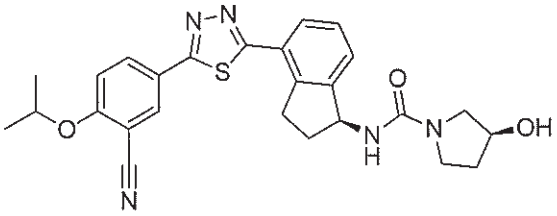
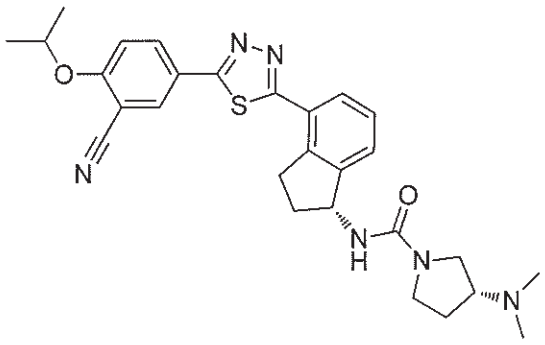

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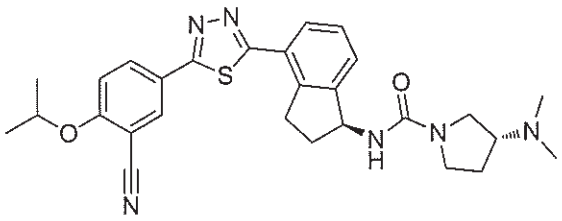
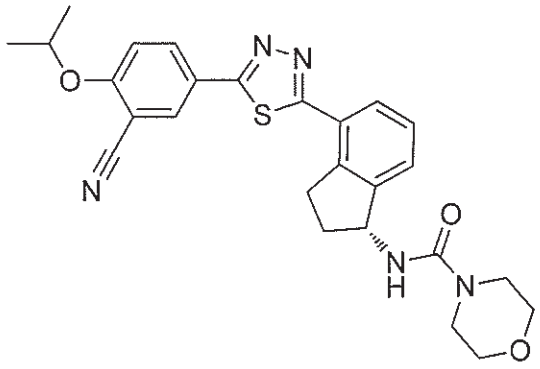
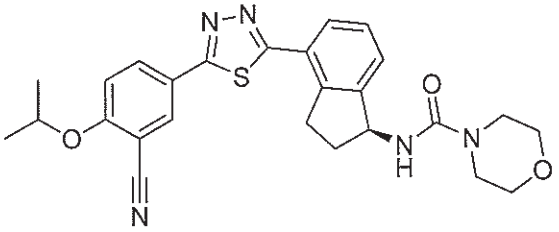
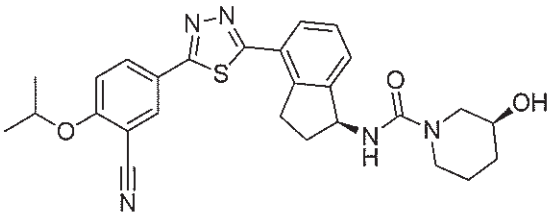
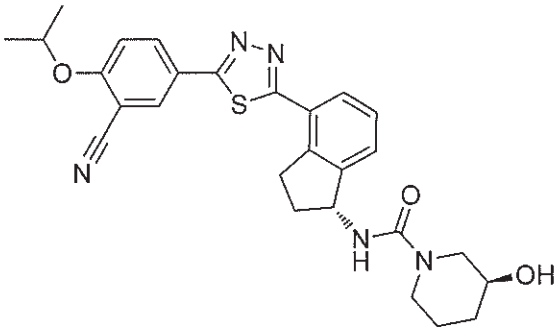
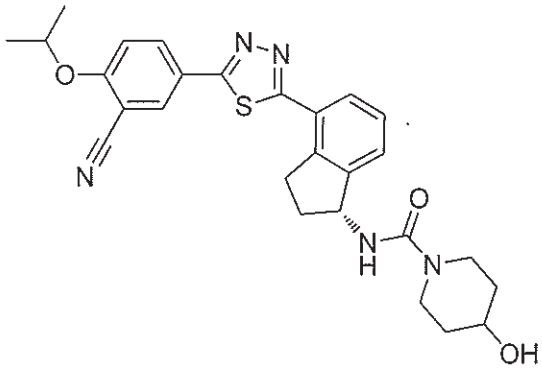
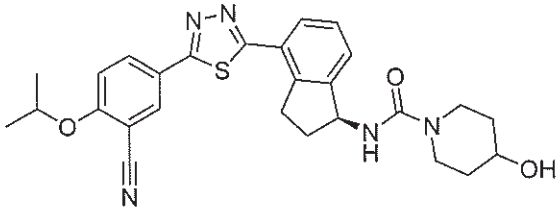
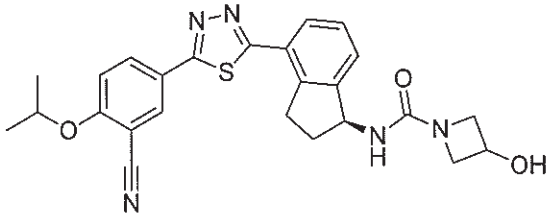

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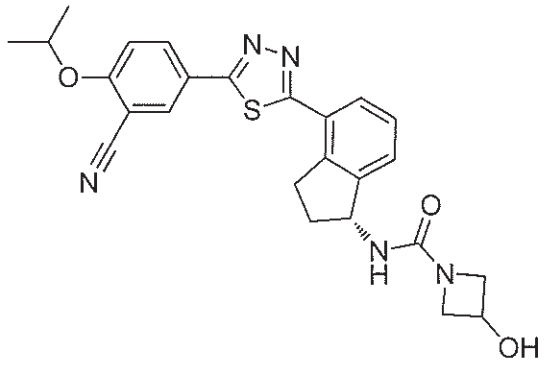
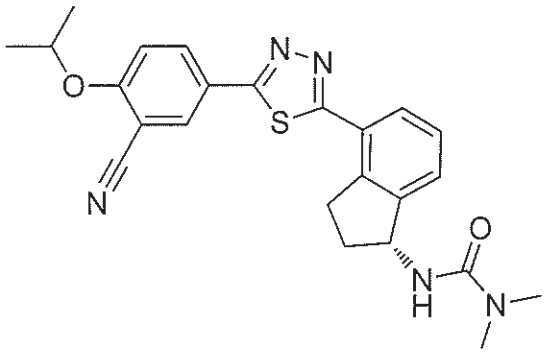
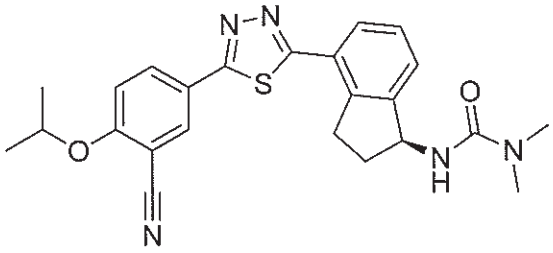
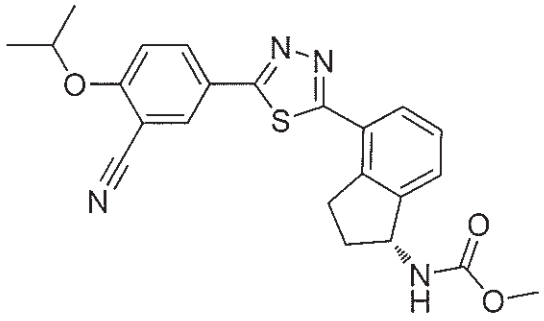
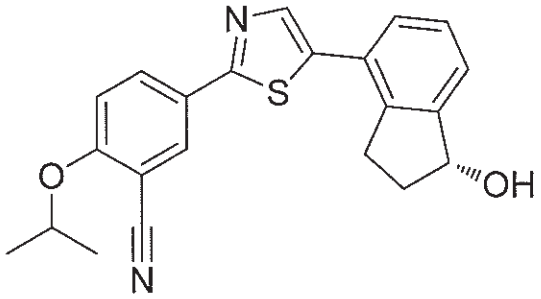
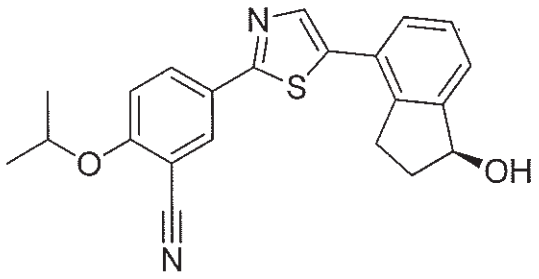
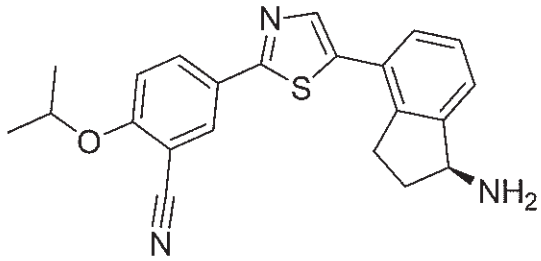
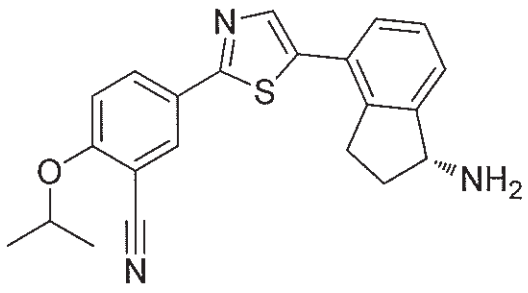

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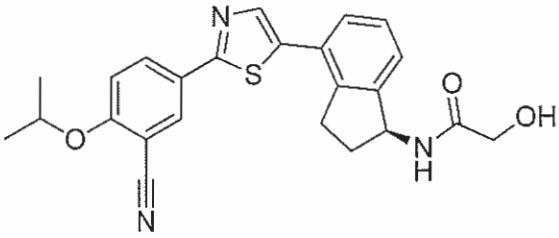
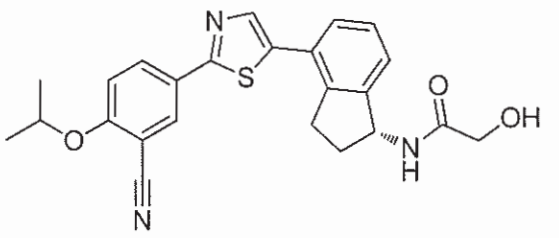
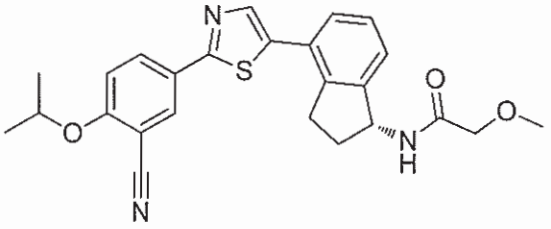
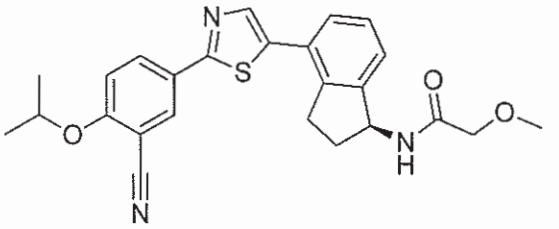
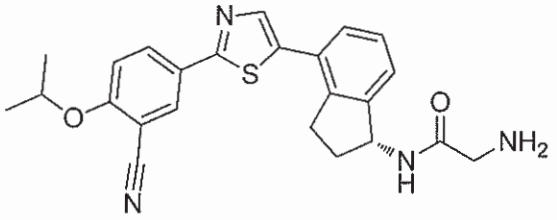
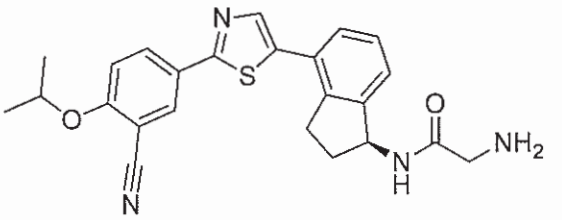
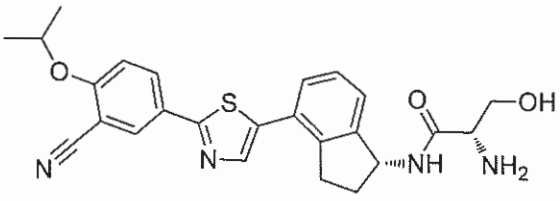
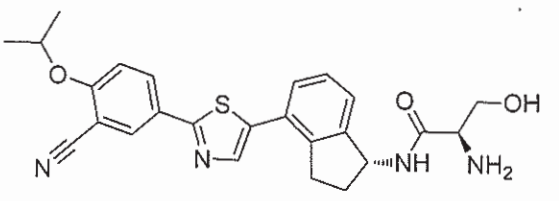
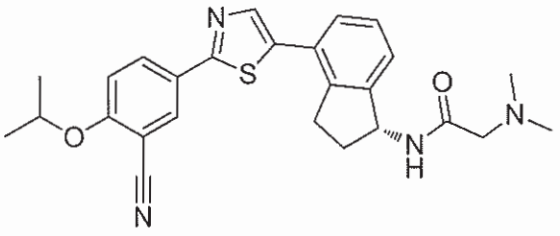
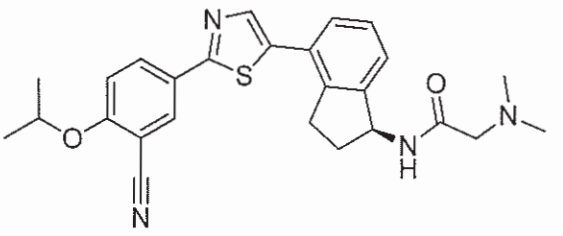
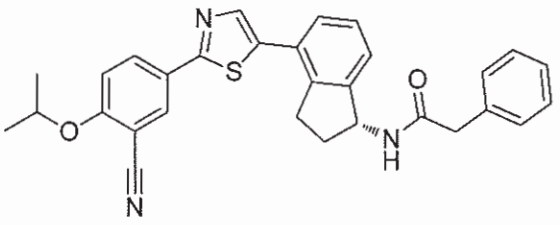
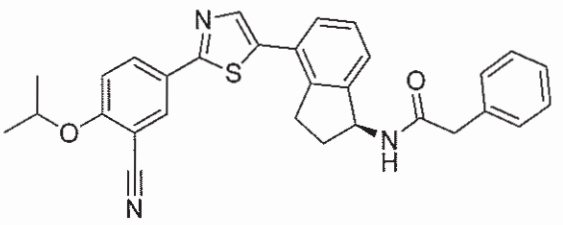

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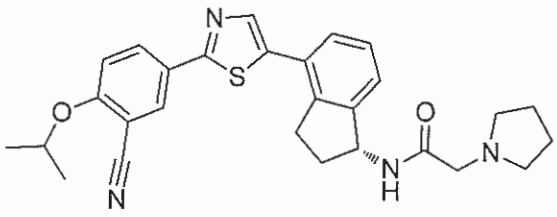
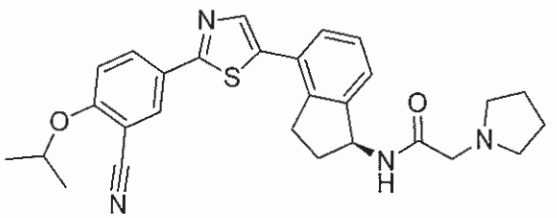
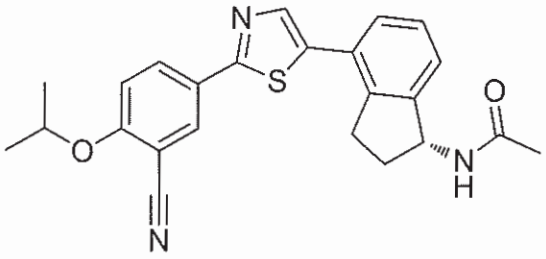
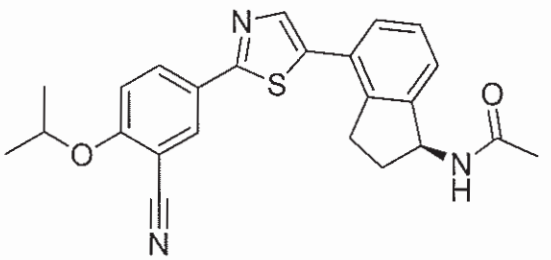
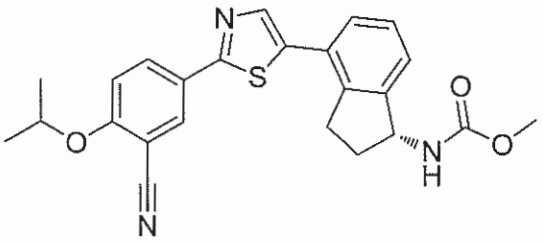
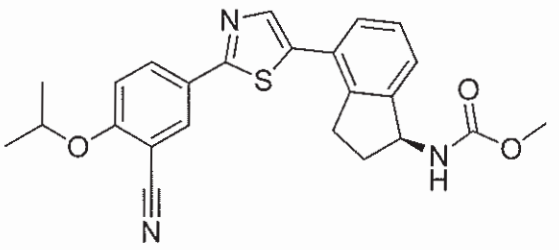
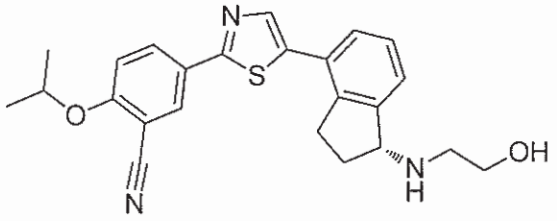
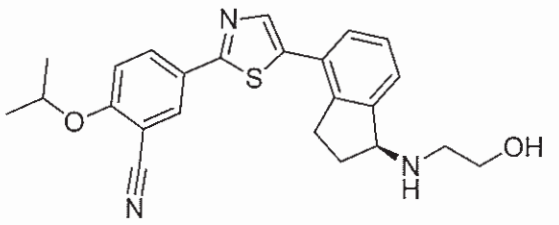
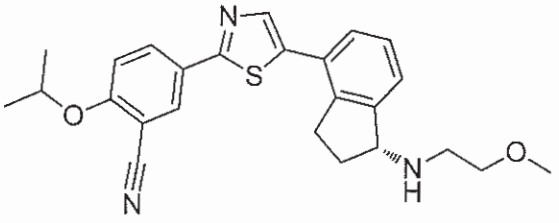
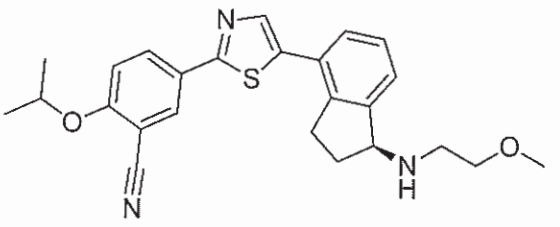
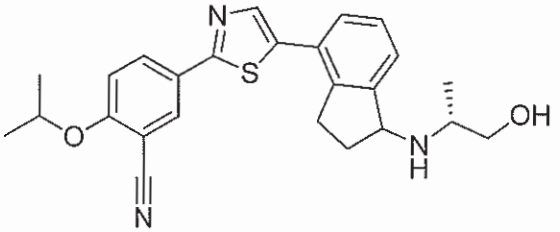
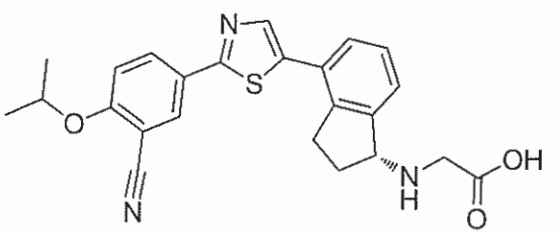

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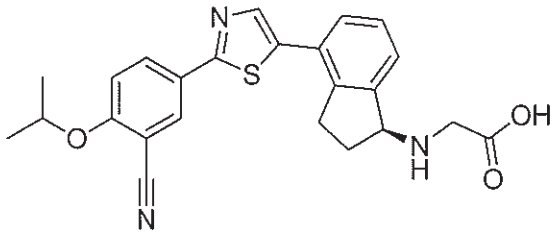
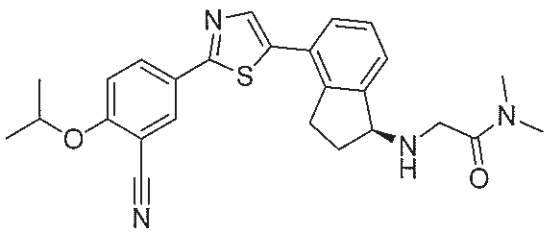
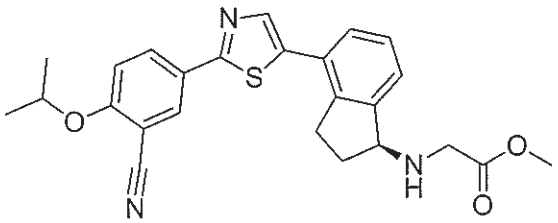
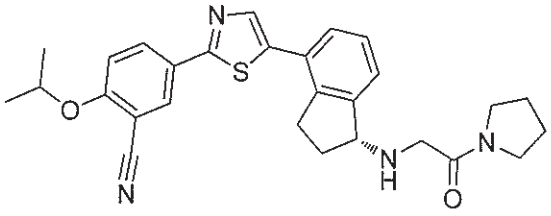
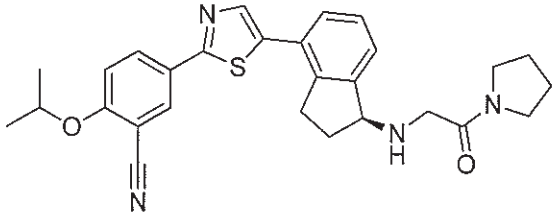
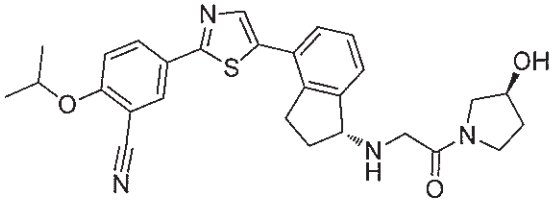
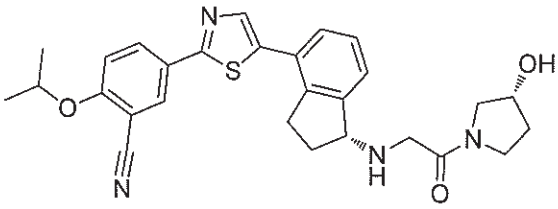
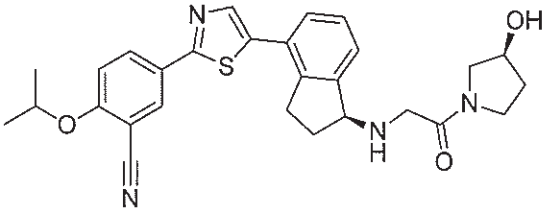
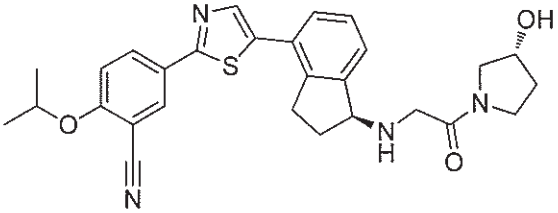
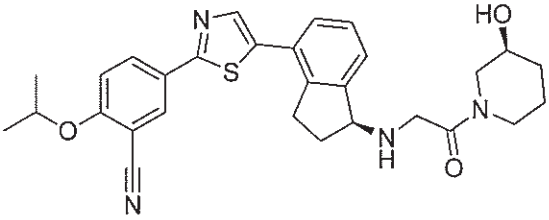
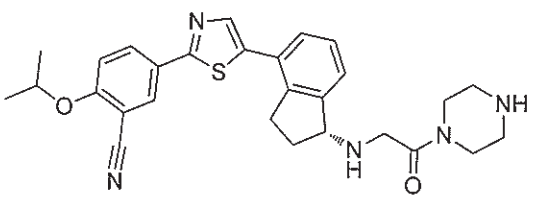
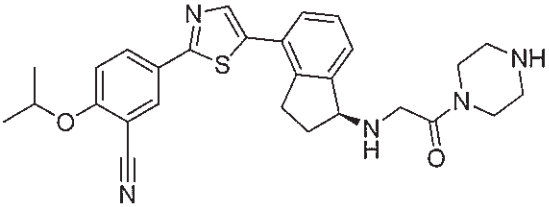

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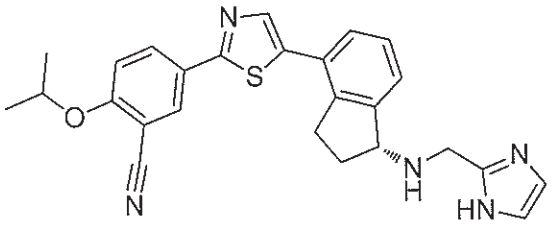
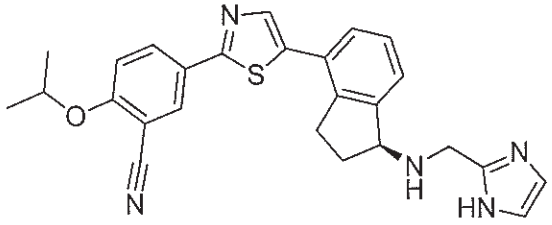
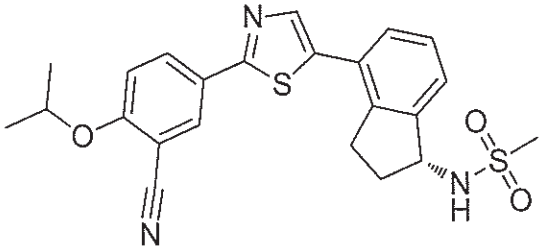
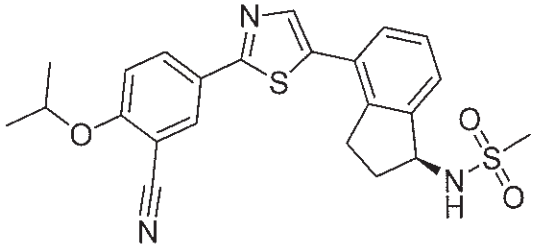
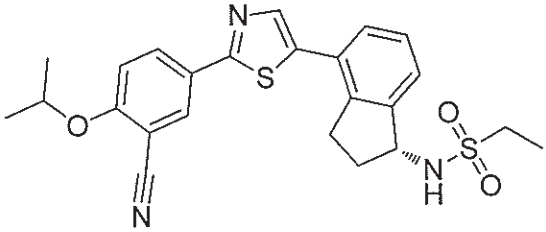
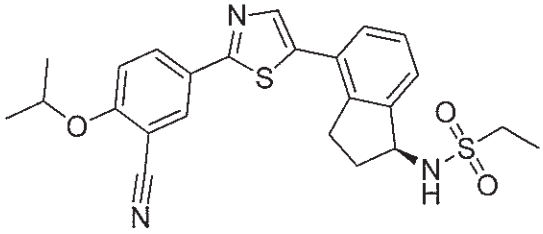
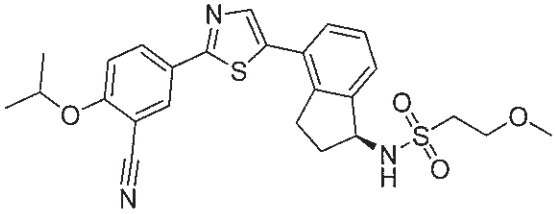
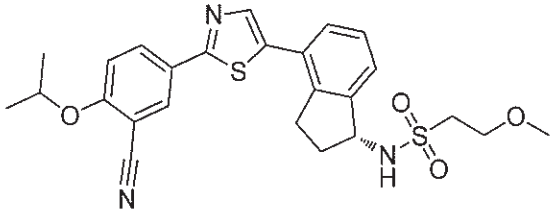
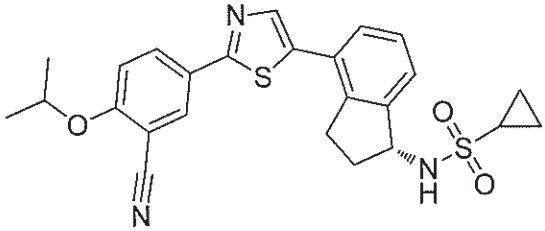
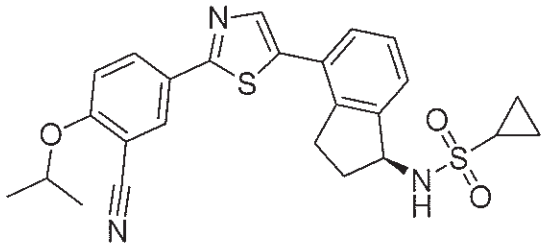
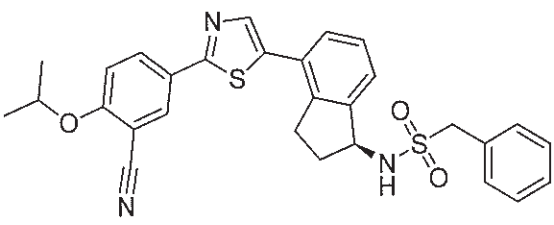
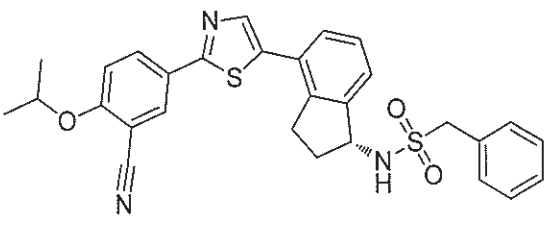

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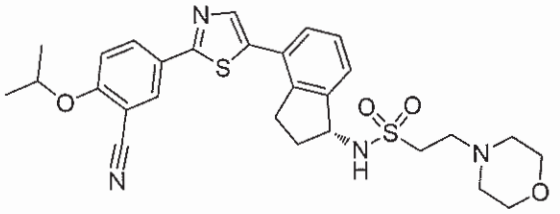
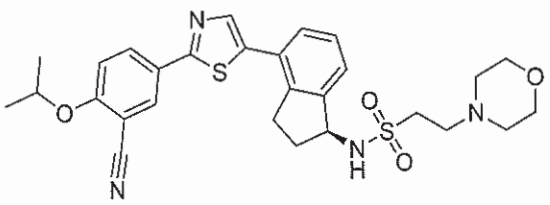
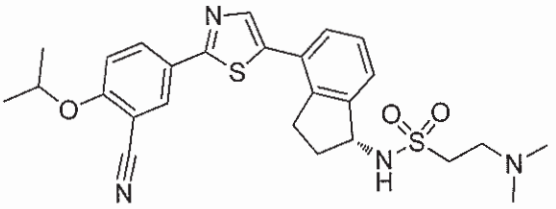
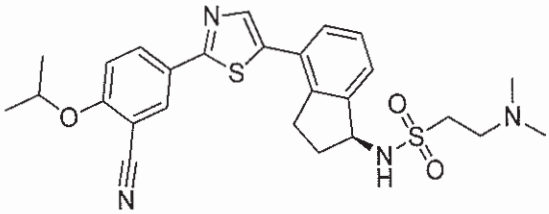
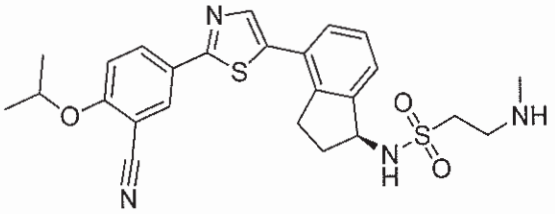
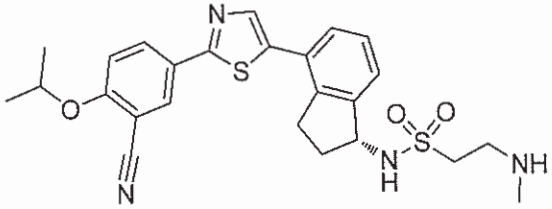
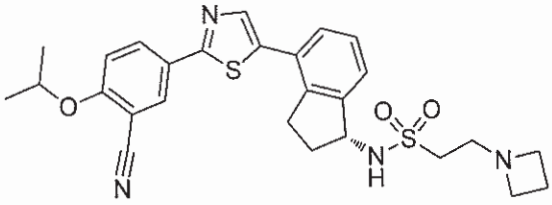
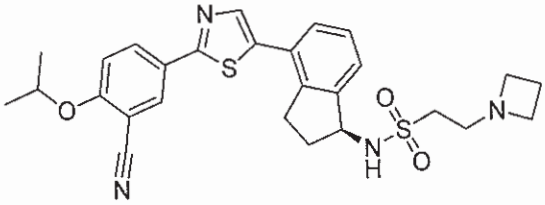
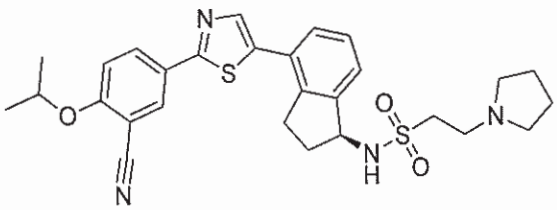
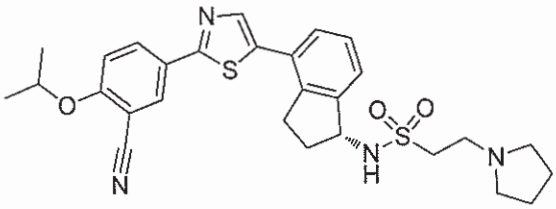
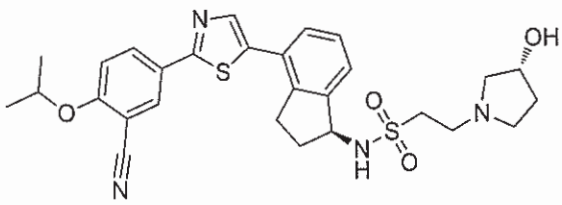
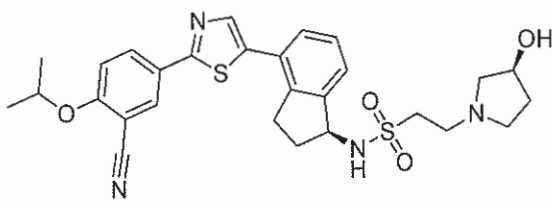

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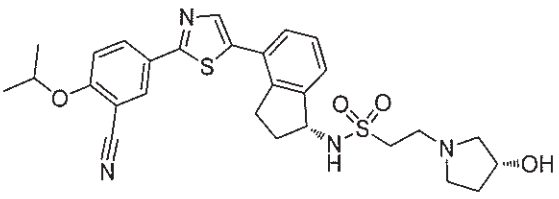
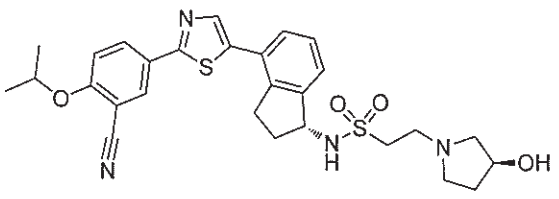
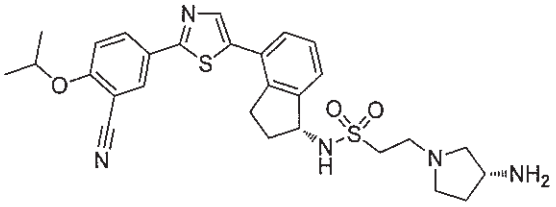
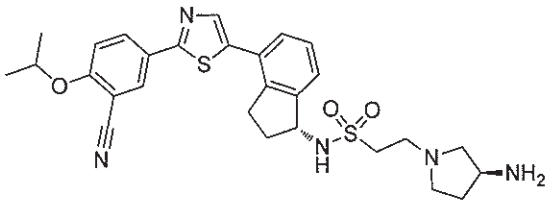
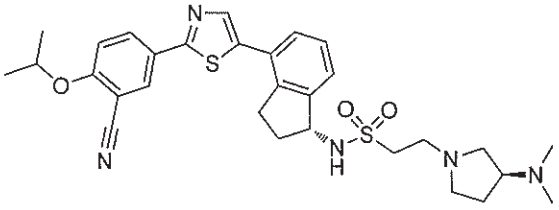
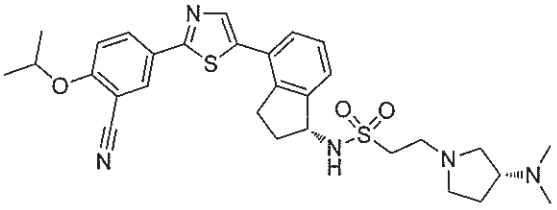
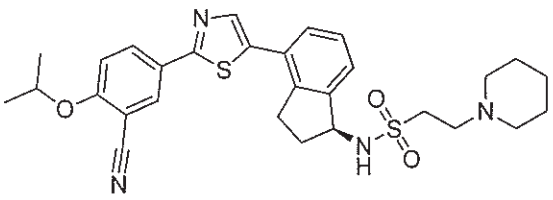
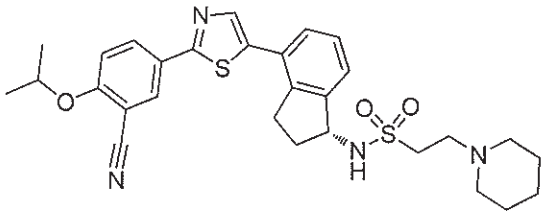
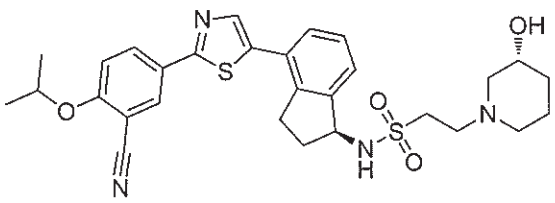
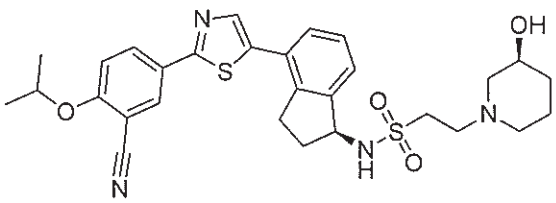
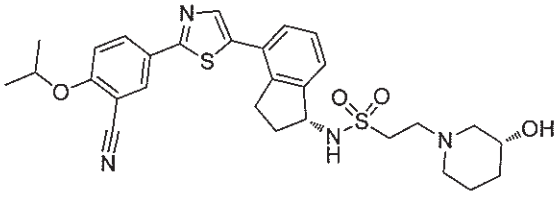
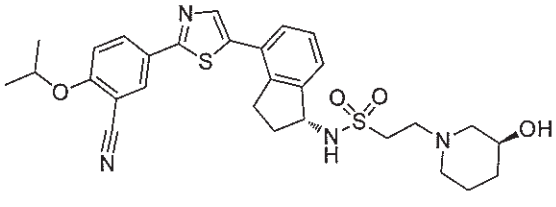
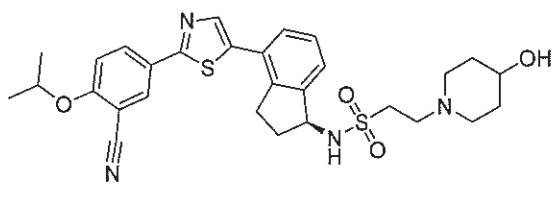
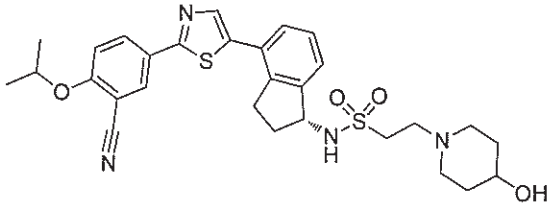
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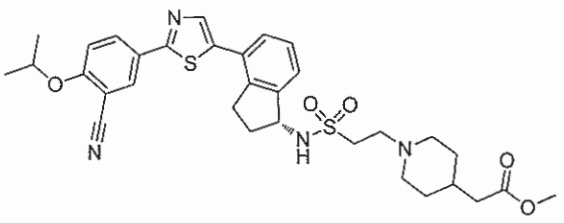
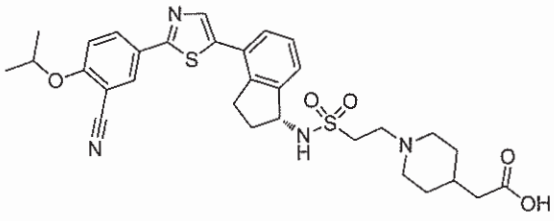
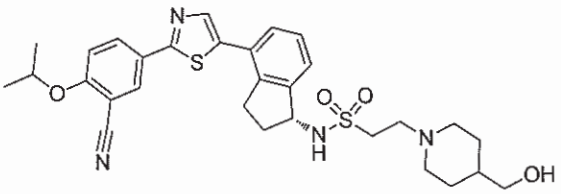
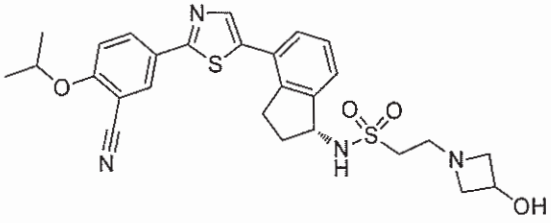
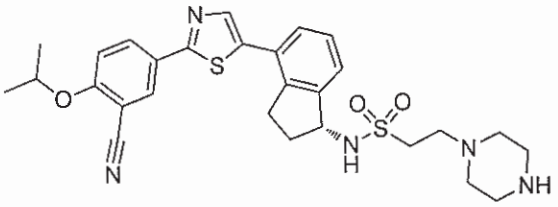
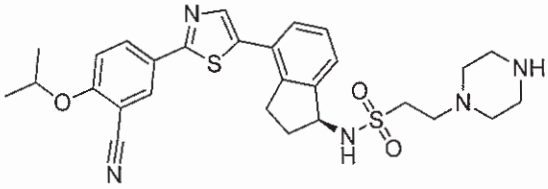
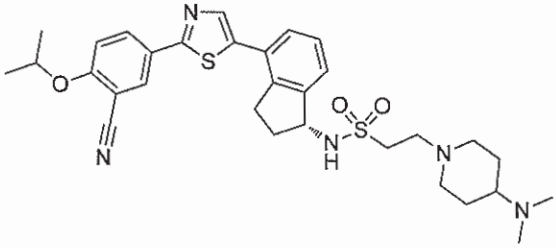
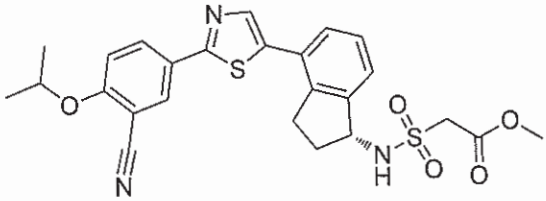
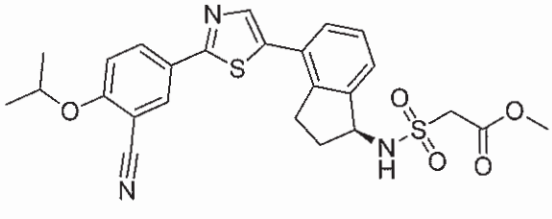
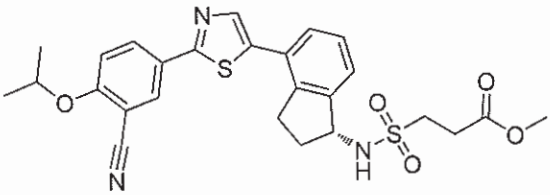
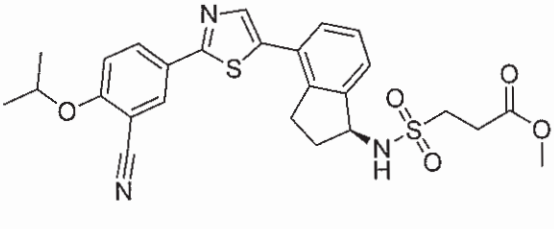
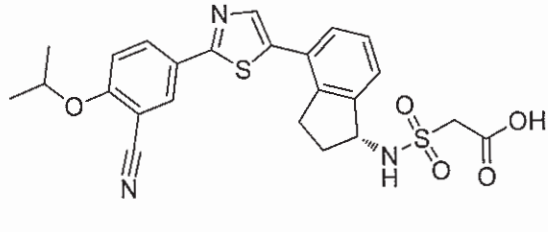
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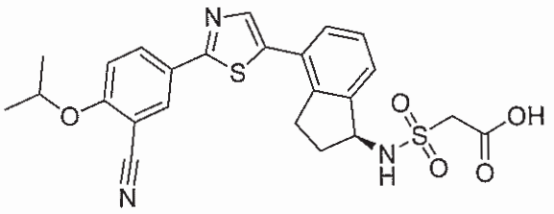
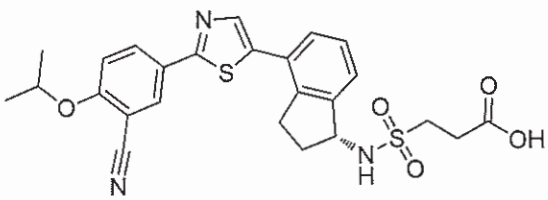
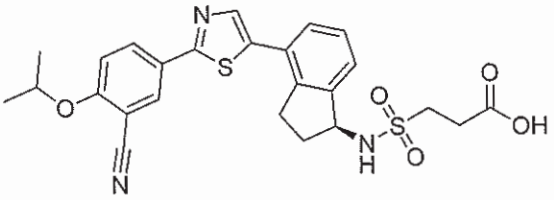
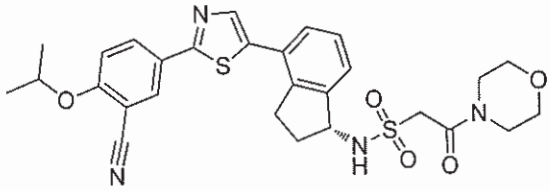
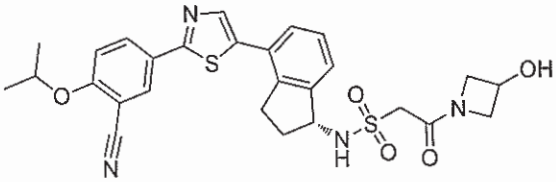
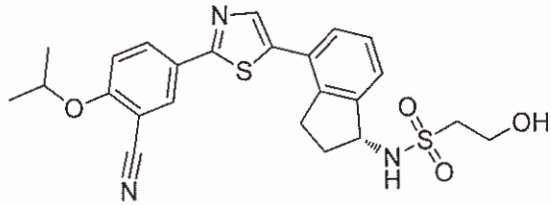
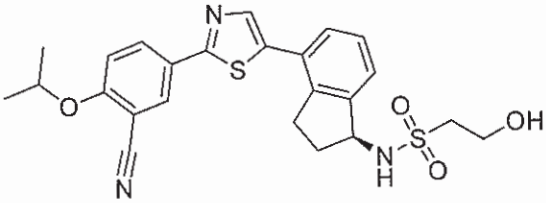
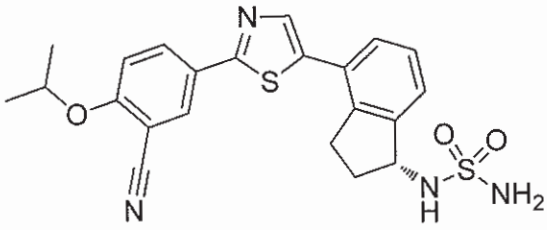
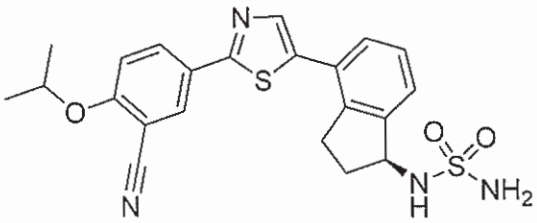
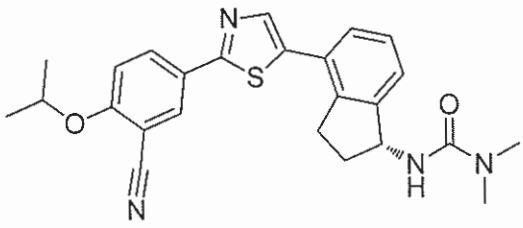
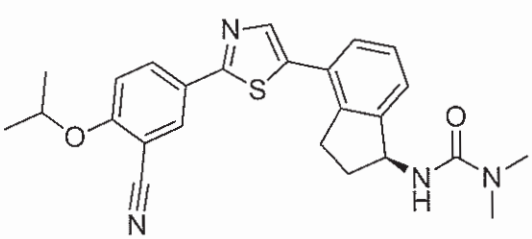
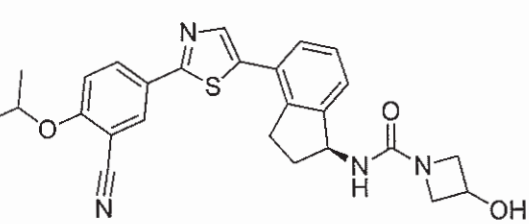
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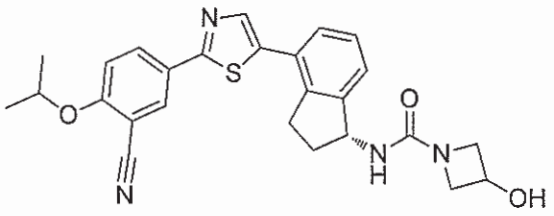
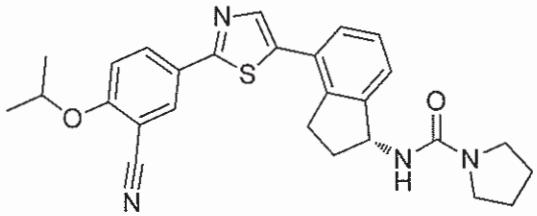
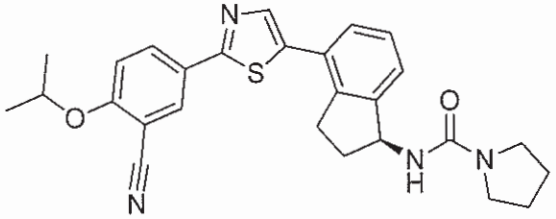
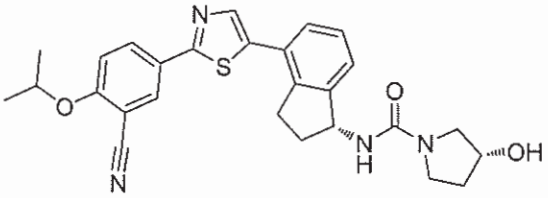
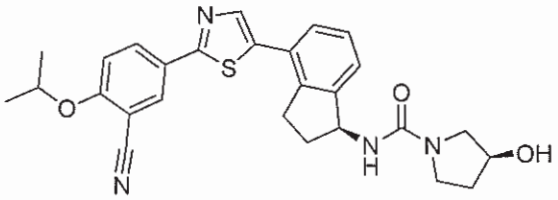
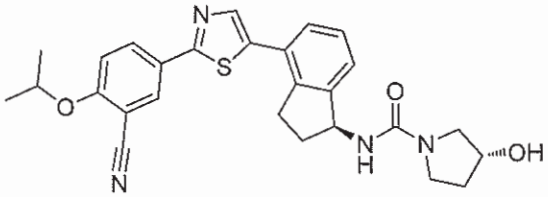
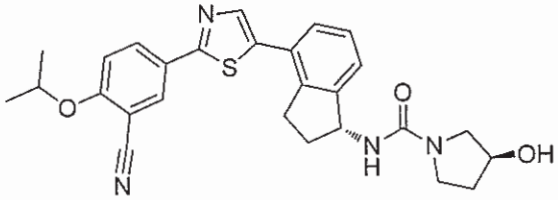
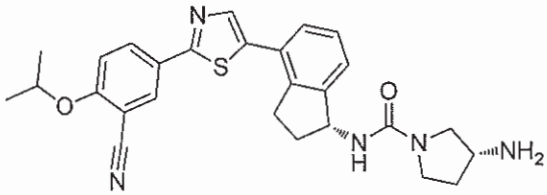
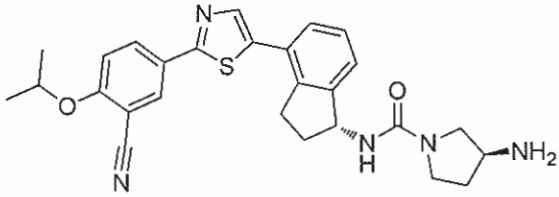
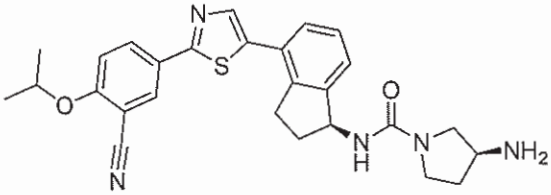
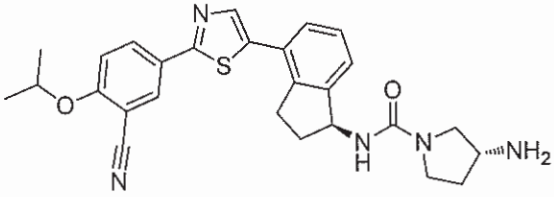
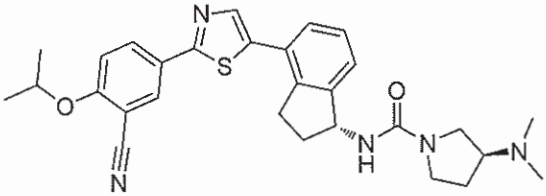
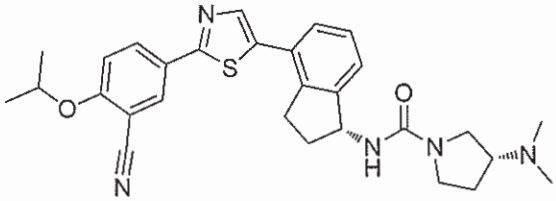
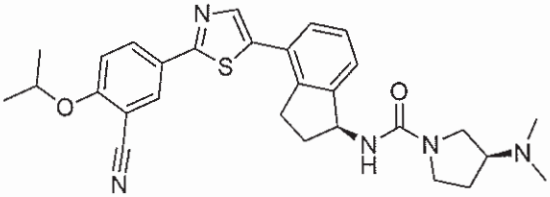
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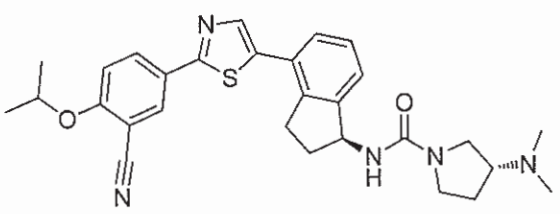
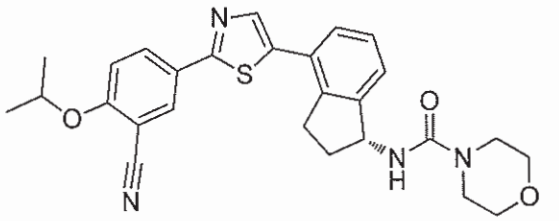
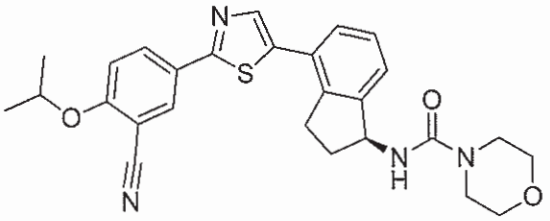
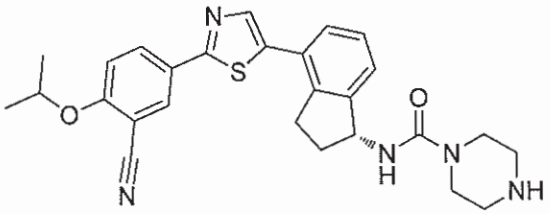
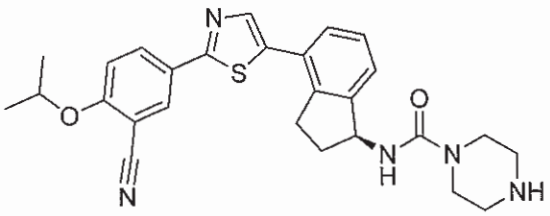
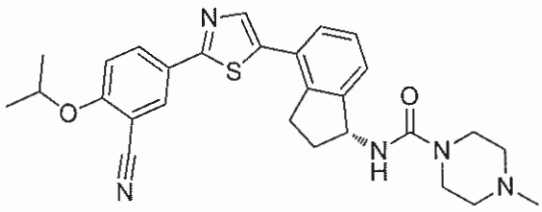
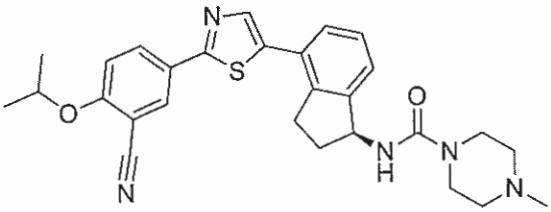
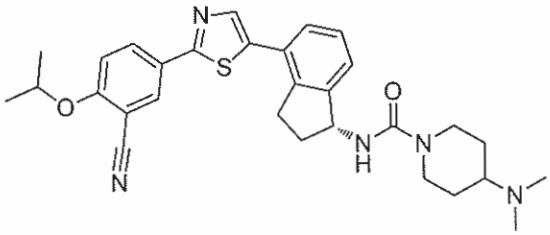
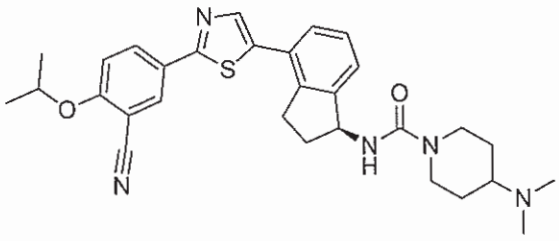
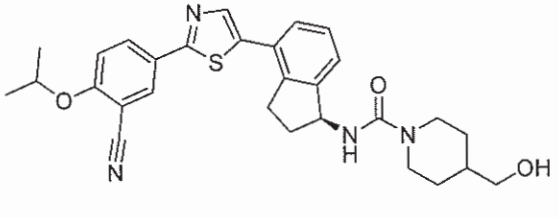
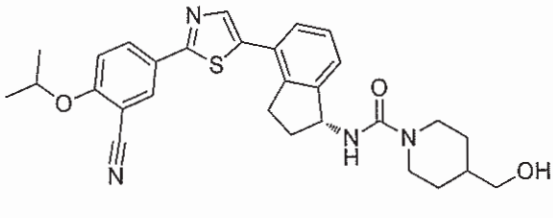
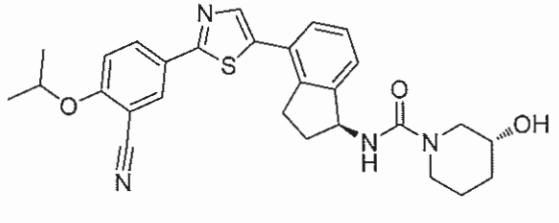
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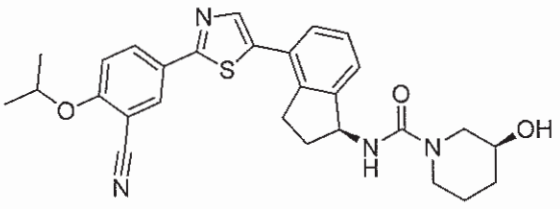
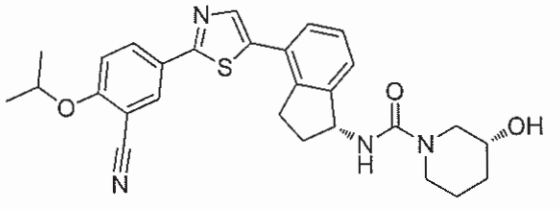
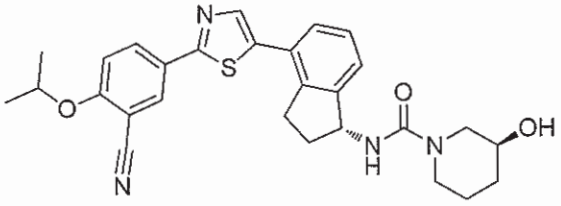
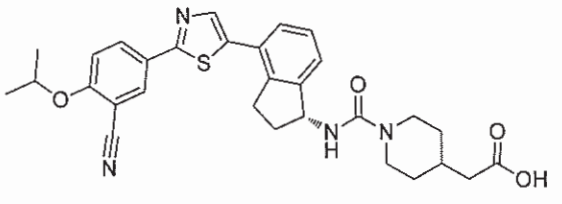
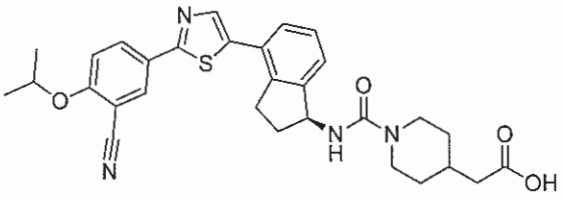
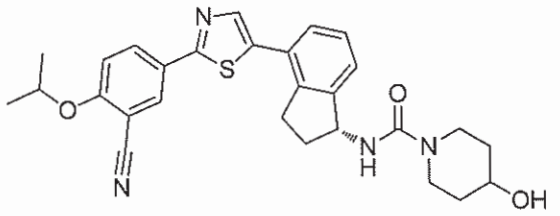
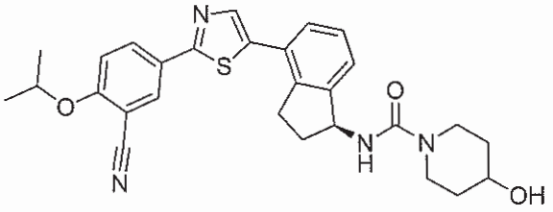
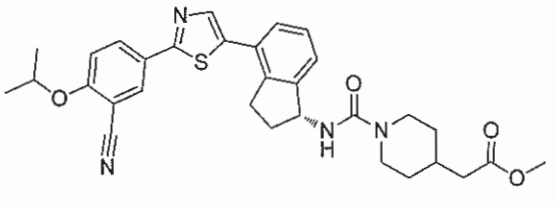
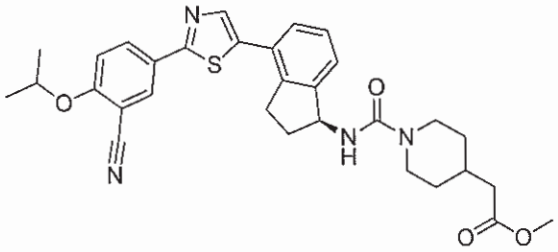
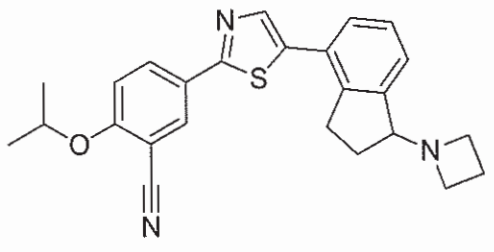
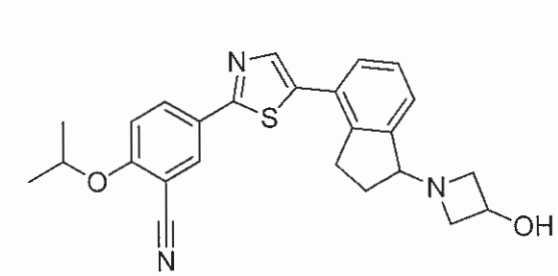
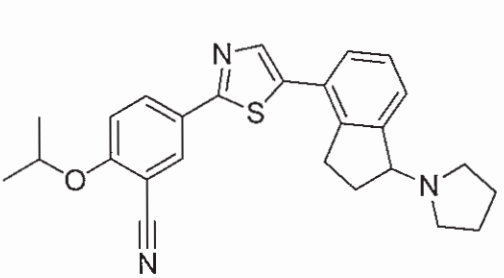
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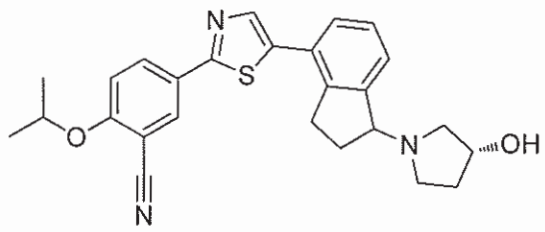
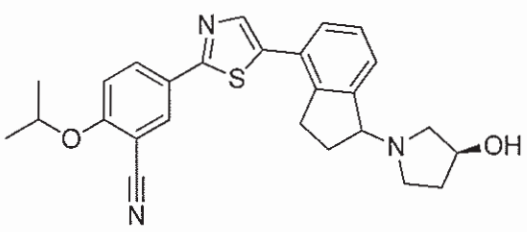
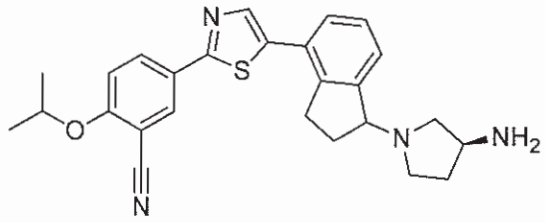
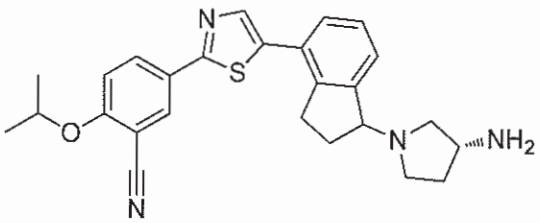
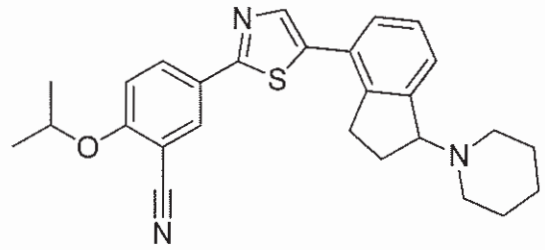
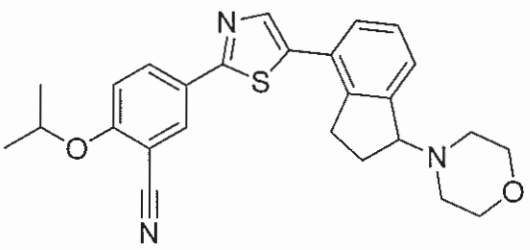
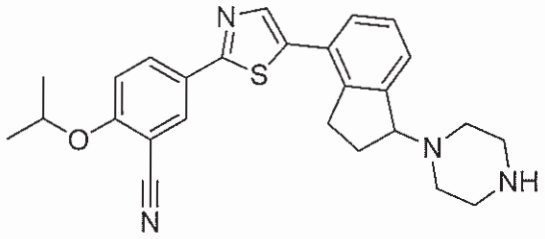
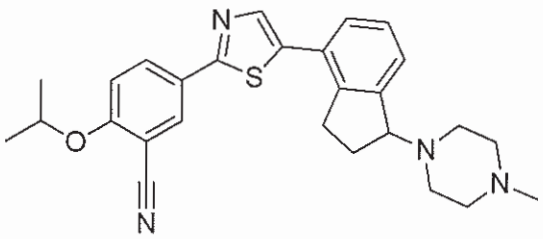
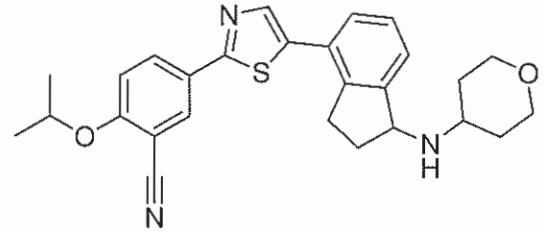
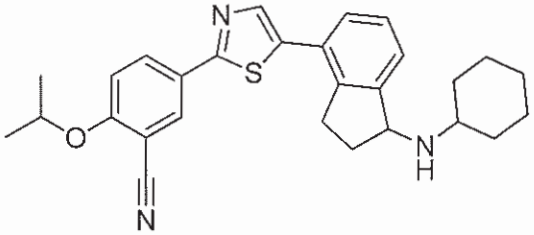
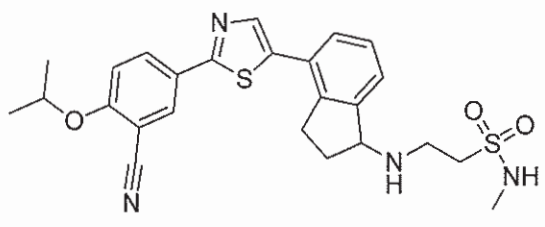
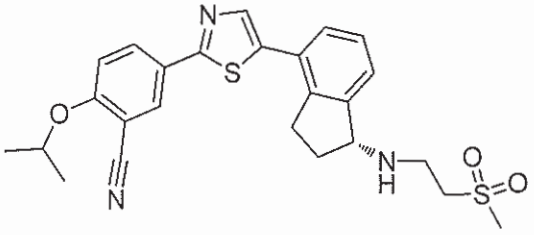
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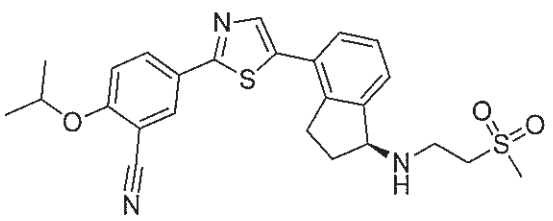
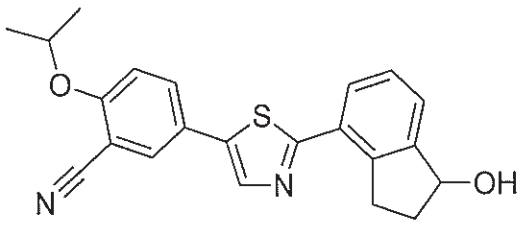
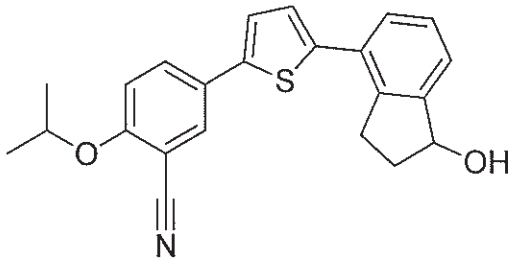
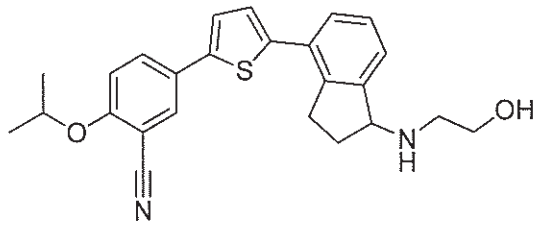
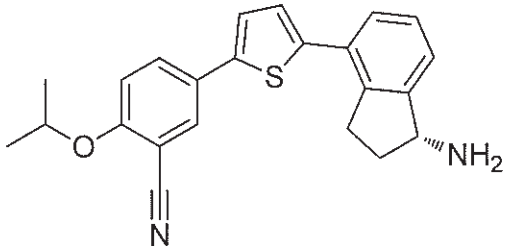
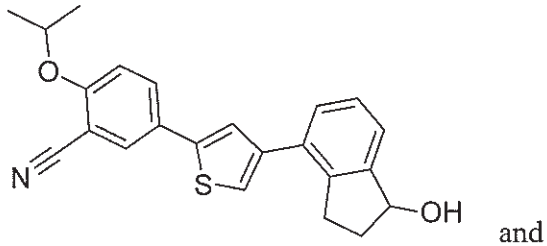
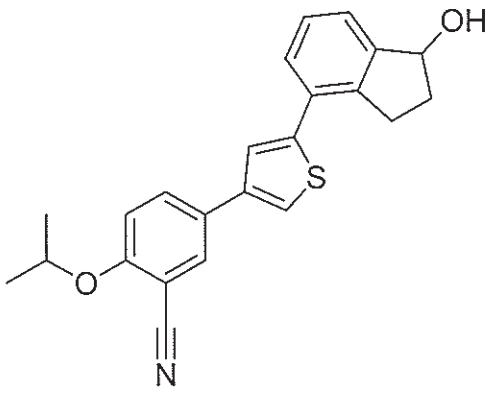

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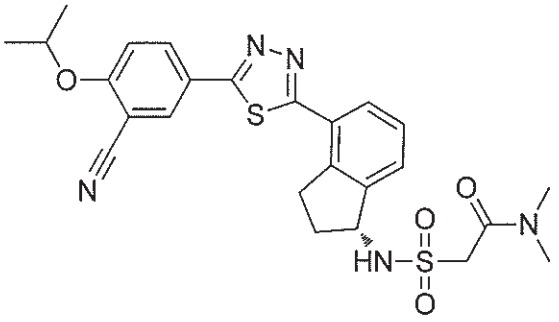
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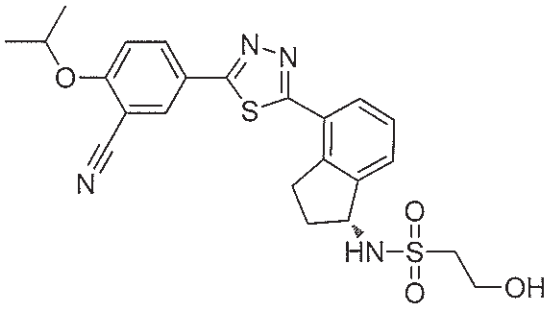

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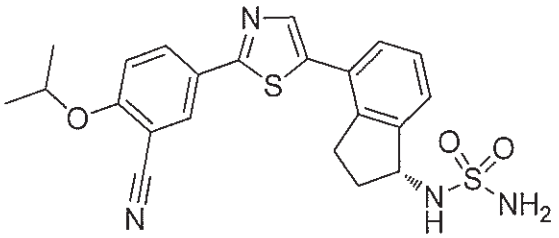

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and

or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof.

51. The compound of claim 50 wherein the compound is selected from:







or any pharmaceutically acceptable salt, ester, prodrug, homolog, tautomer, stereoisomer, or hydrate, or solvate thereof.

52. A pharmaceutical composition comprising the compound as in any one of claims 1-51 and a suitable excipient.

53. A pharmaceutical composition comprising the compound as in any one of claims 1-51 and a second medicament.

54. The composition of claim 53 wherein the second medicament is medically indicated for the treatment of multiple sclerosis, transplant rejection, or acute respiratory distress syndrome.

55. The compound of claim 15 wherein the compound is substantially enantiomerically pure.