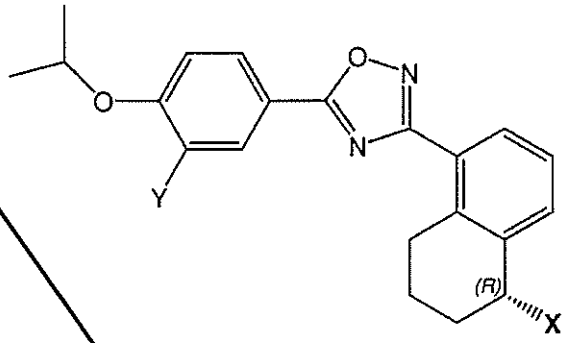
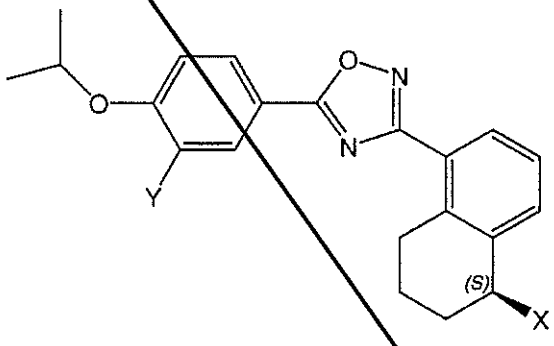
We claim:

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



I-R



I-S

wherein

X is –NR′R″ or -OR‴;

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

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

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

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

R''' is H, C_{1-4} alkyl, or -CO-R^1;

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

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

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

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

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

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

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

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

5. The compound of claims 1-4 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.

6. The compound of claim 5 wherein the therapeutic index is at least 10.

7 The compound of claim 5 wherein the therapeutic index is at least 20.

8. The compound of claims 5-7 wherein the therapeutic index for the compound is greater than the therapeutic index for the enantiomer of the compound.

9. The compound of claim 8 wherein the therapeutic index for the compound is at least 150% of the therapeutic index for the enantiomer of the compound.

10. The compound of claims 1-9 wherein Y is Cl.

11. The compound of claims 1-9 wherein Y is CF_3.

12. The compound of claims 1-9 wherein Y is CN.

13. The compound of claims 1-12 wherein X is –NR′R″.

14. The compound of claims 1-12 wherein X is –OR‴.

15. The compound of claim 14 wherein X is –OH.

16. The compound of claim 14 wherein X is –OCO-R^1.

17. The compound of claim 16 wherein R^1 is C_{1-3} alkyl.

18. The compound of claim 13 wherein R′ is H.

19. The compound of claim 13 wherein R′ is -COR^1.

20. The compound of claim 13 wherein R′ is -SO_2-R^1.

21. The compound of claim 13 wherein R″ is H.

22. The compound of claim 13 wherein R″ is -SO_2-R^3.

23. The compound of claim 13 wherein R″ is C_{1-4} alkyl optionally substituted with 1 or more R^2.

24. The compound of claim 13 wherein R″ is –$(CR^aR^b)_n$-R^2 ; each R^a and each R^b is independently selected from the group consisting of H, hydroxyl and methyl or R^a and R^b bound to the same carbon taken together are oxo; and n is 0, 1, 2, or 3.

25. The compound of claim 24 wherein n is 2.

26. The compound of claim 25 wherein R^2 is –OH, -NH_2, -NHR^1, -$N(R^5R^5)$, or –COOH.

27. The compound of claim 22 wherein R^3 is C_{1-4} alkyl optionally substituted with 1 or more R^2.

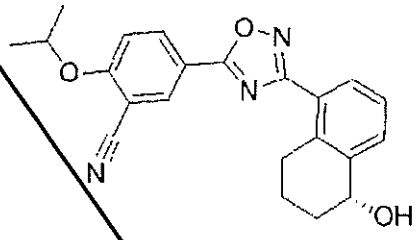
28. The compound of claim 22 wherein Y is CN.

29. The compound of claim 27 wherein R^3 is –C_2H_5-N((R^5R^5) or –CH_2-CO-N(R^5R^5).

30. The compound of claim 28 wherein R^3 is C_2H_5–O-R^1.

31. The compound of claim 12 wherein X is –NH-CO-N(R^5R^5).

32. The compound of claim 1 wherein the compound is selected from **compounds 1-55**: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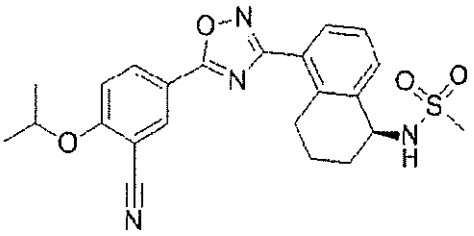
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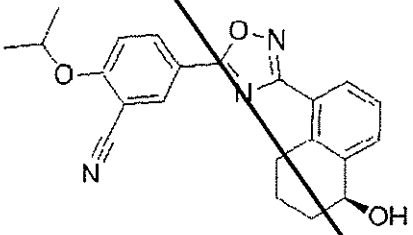
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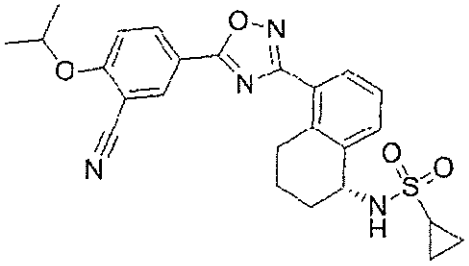
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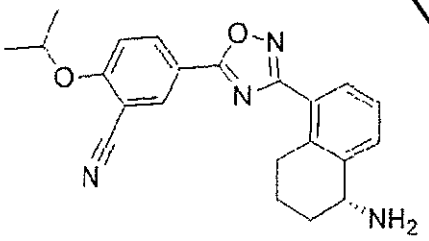
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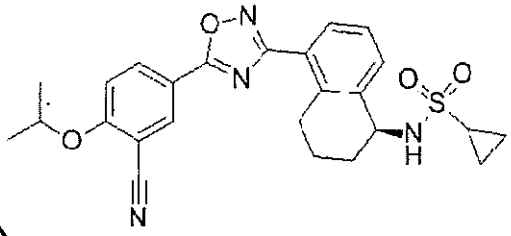
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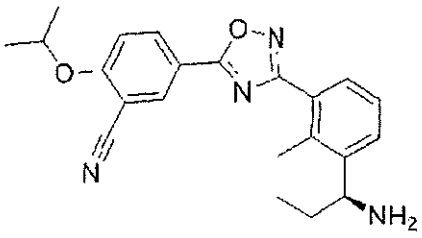
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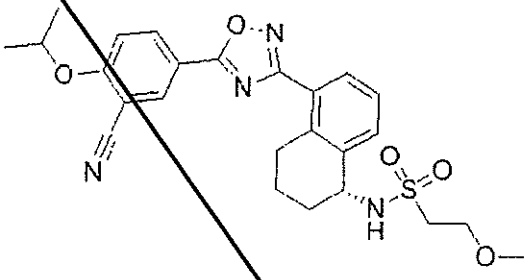
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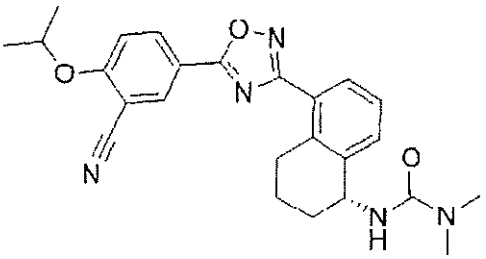
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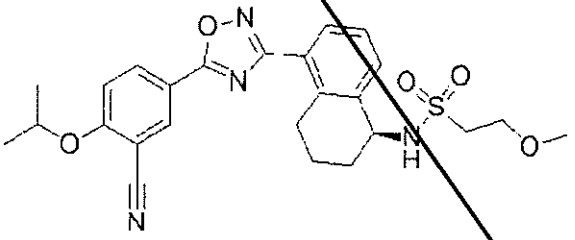
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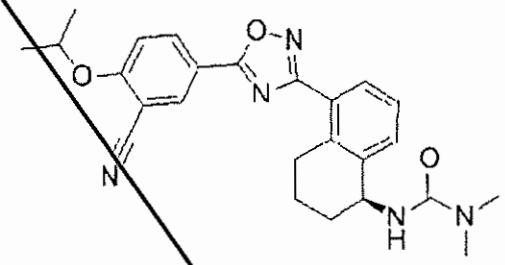
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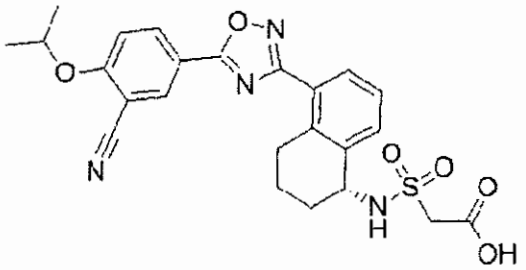
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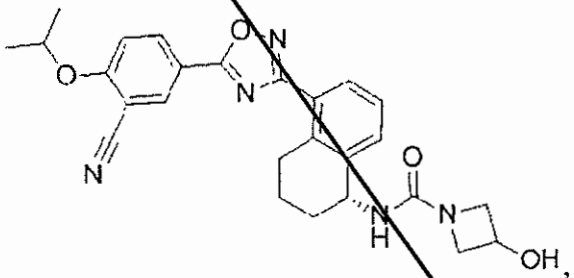
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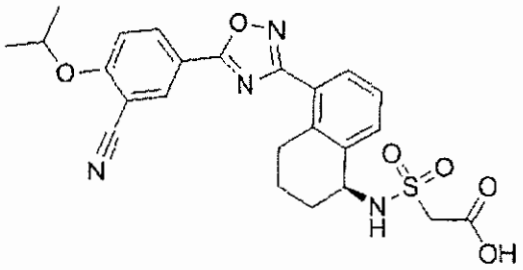
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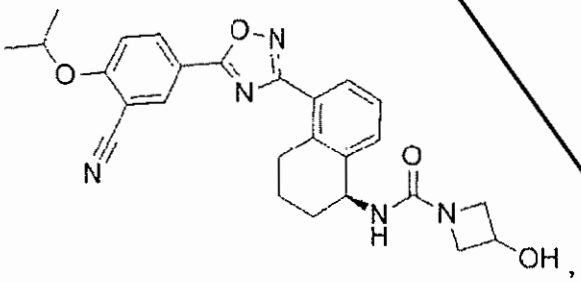
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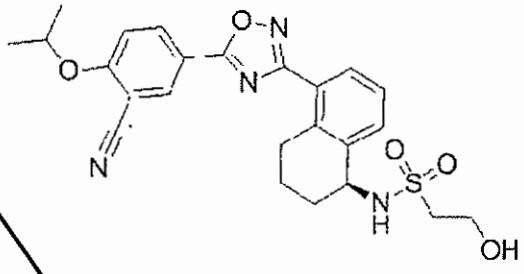
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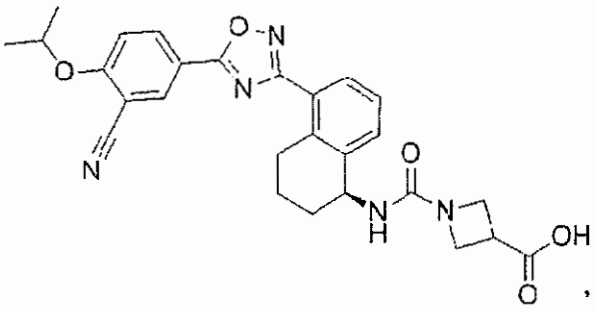
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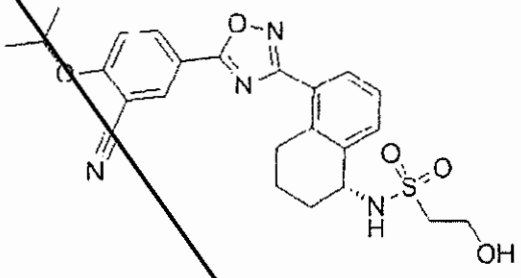
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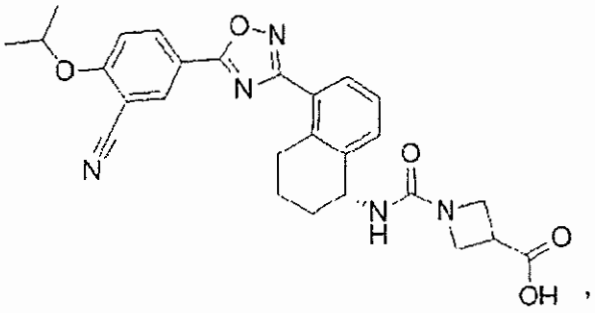
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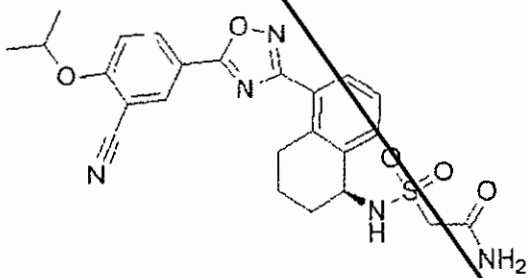
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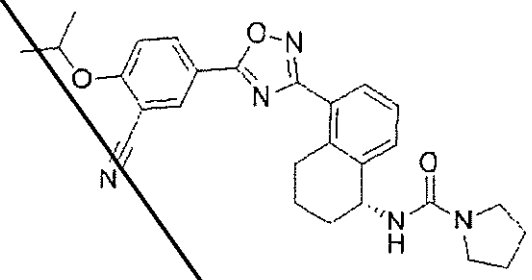
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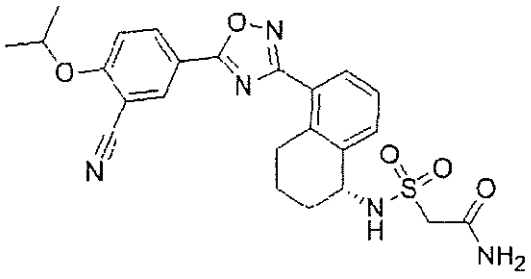
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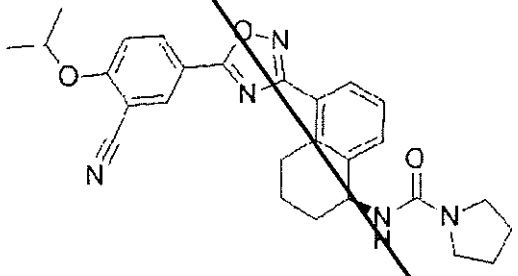
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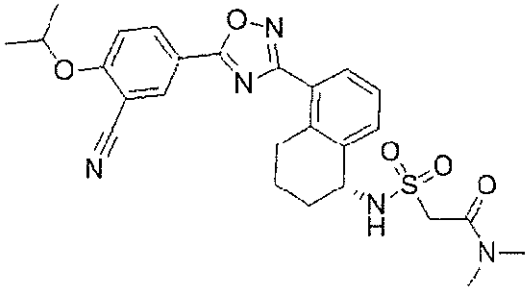
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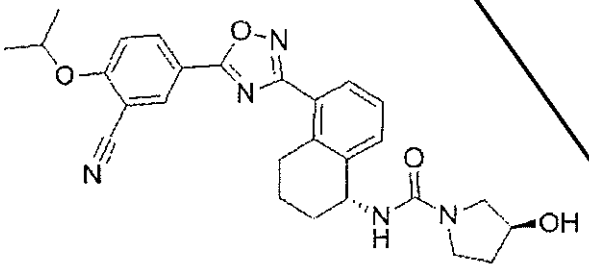
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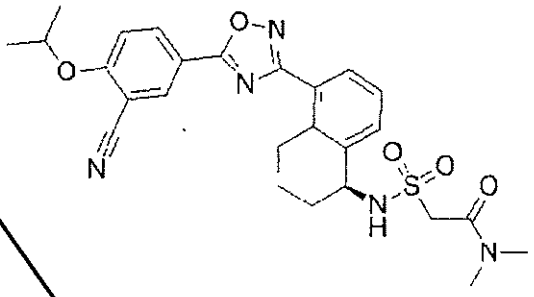
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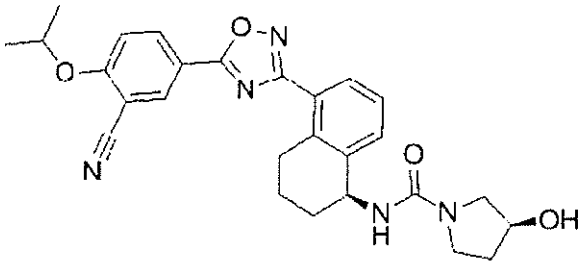
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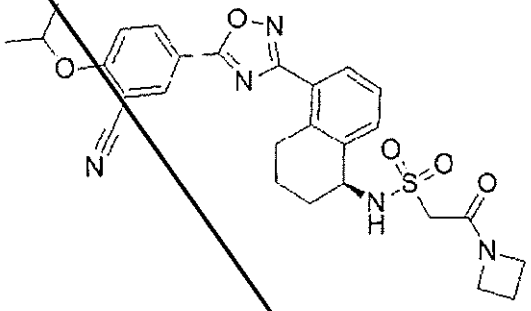
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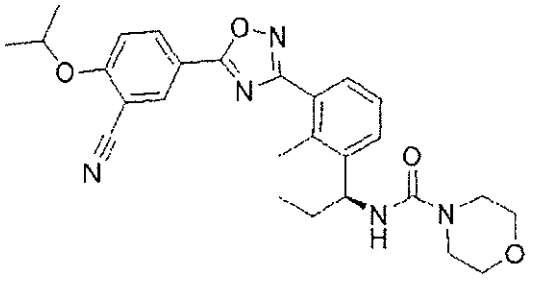
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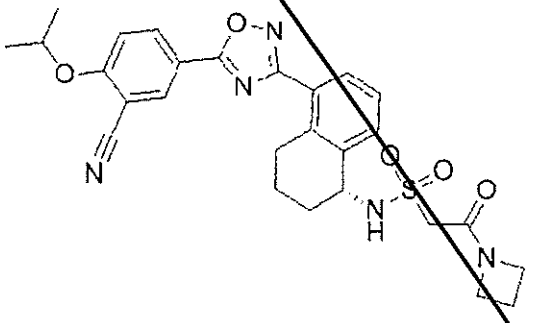
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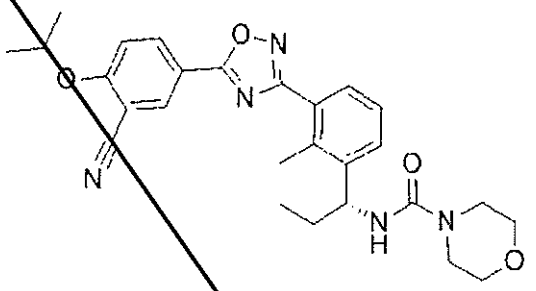
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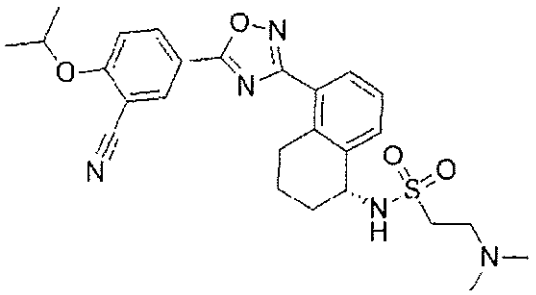
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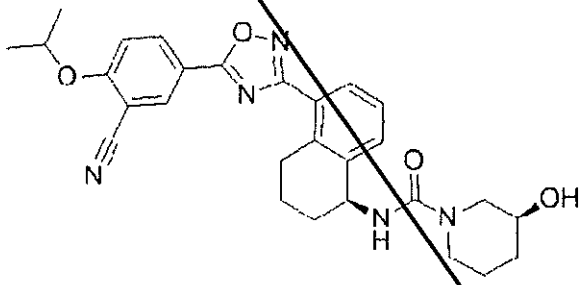
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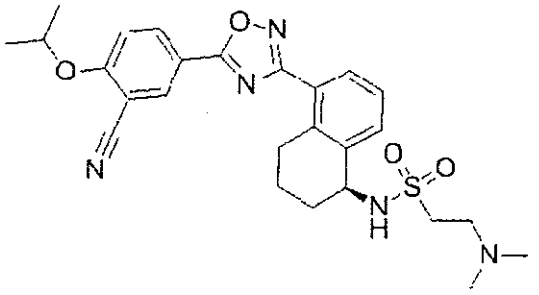
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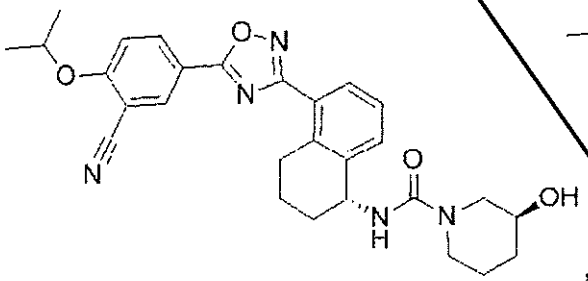
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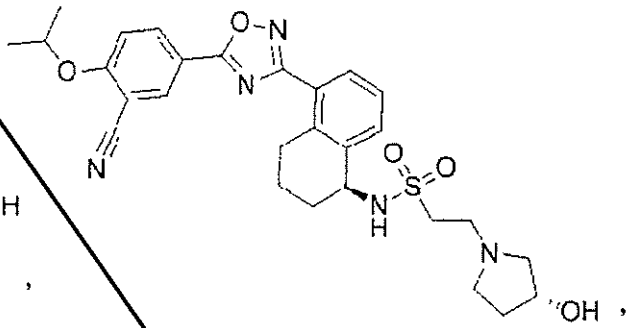
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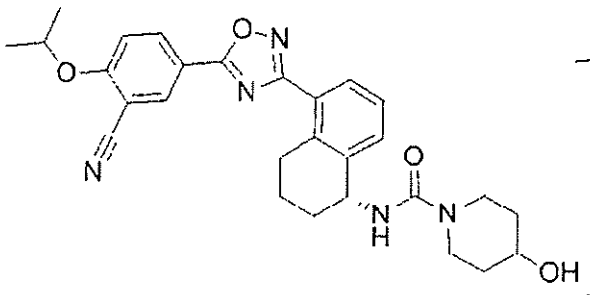
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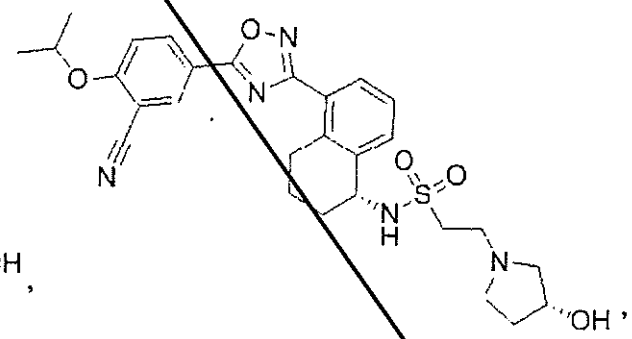
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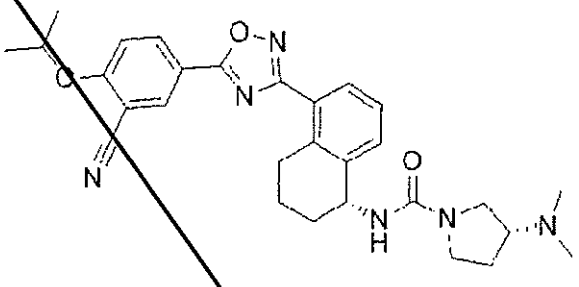
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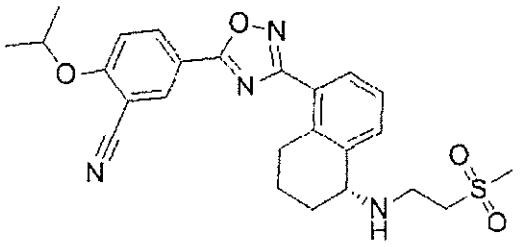
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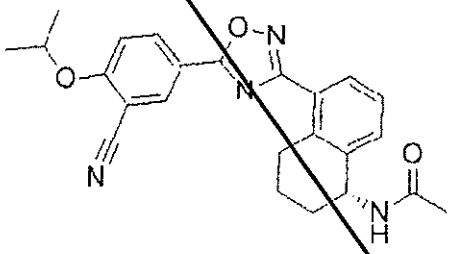
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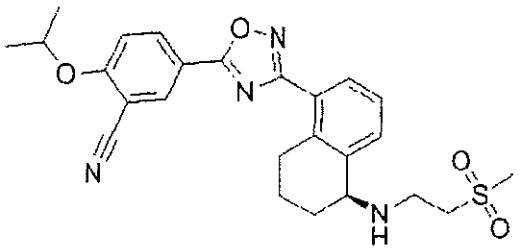
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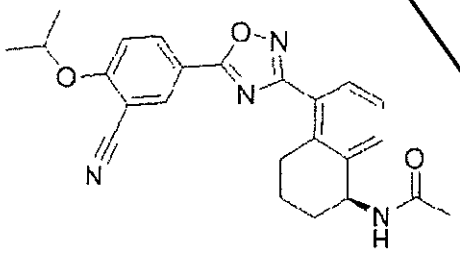
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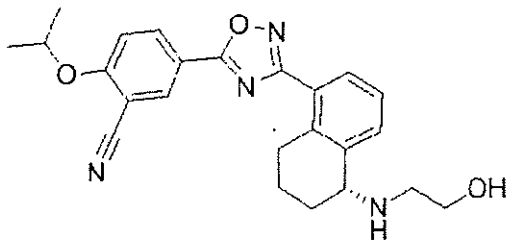
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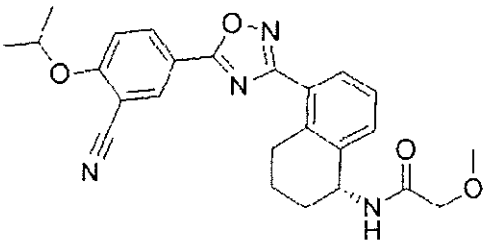
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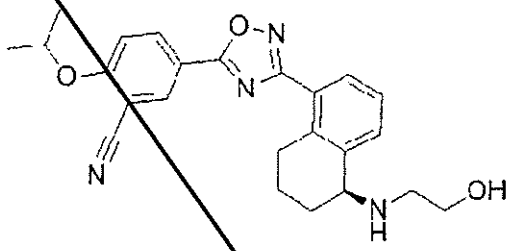
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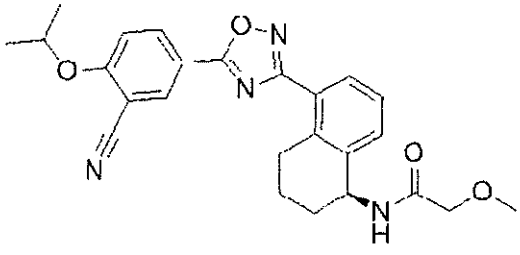
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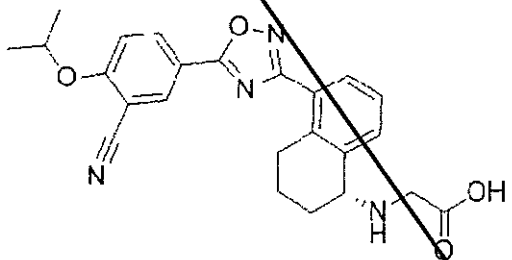
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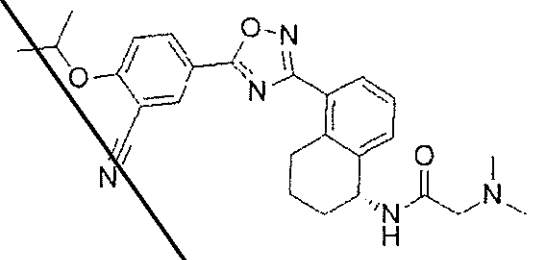
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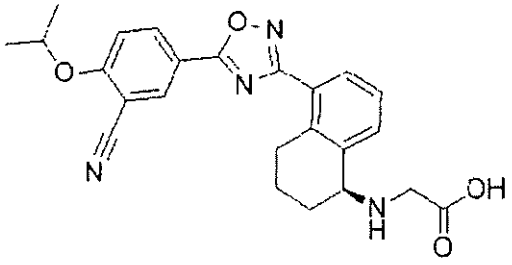
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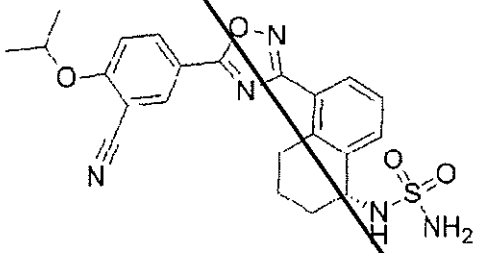
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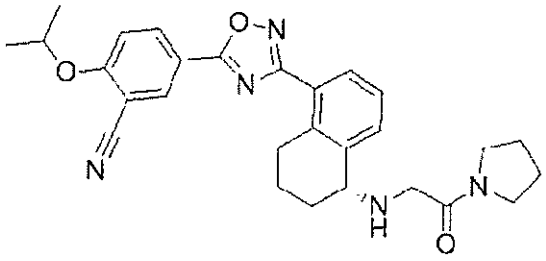
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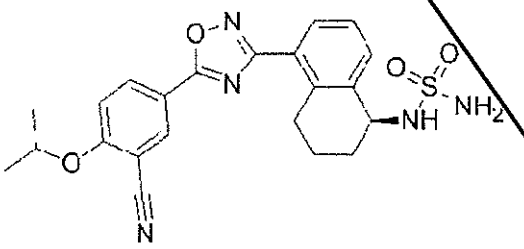
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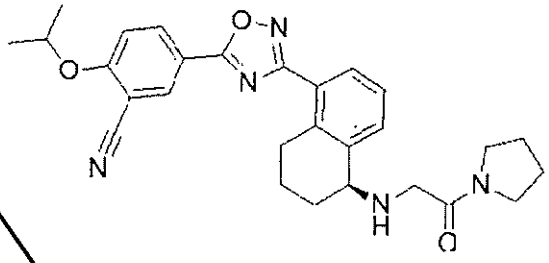
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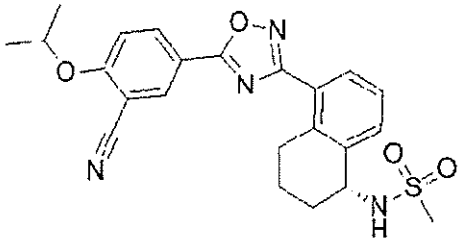
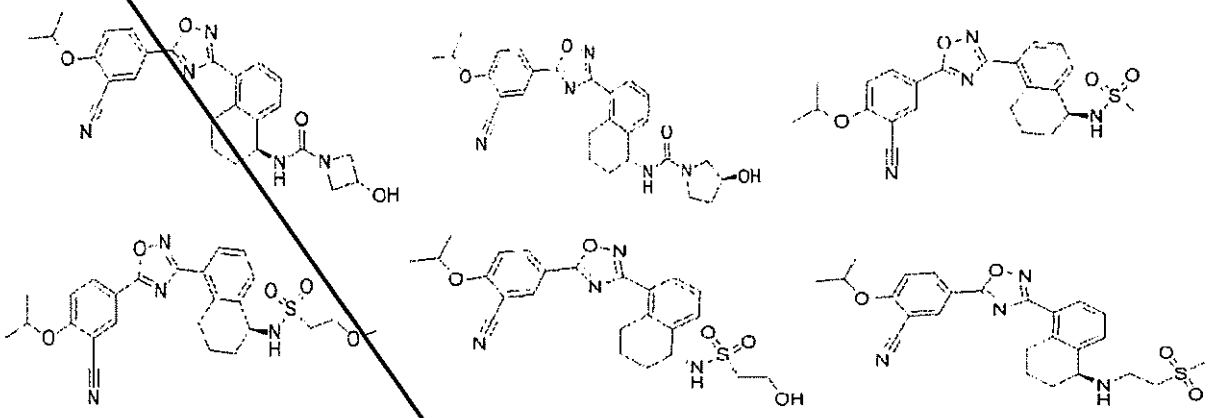

and .

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

33. The compound of claim 32 selected from the group consisting of compounds 8, 13, 29, 33, 37, and 49:



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

34. A pharmaceutical composition comprising a compound of claims 1-33 and a suitable excipient.

35. A pharmaceutical combination comprising the compound of claims 1-33 and a second medicament.

36. The combination of claim 35 wherein the second medicament is medically indicated for the treatment of multiple sclerosis, transplant rejection, or acute respiratory distress syndrome.

37. The use of a compound of any one of claims 1-33 for preparation of a medicament.

38. 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 1-33 or the composition of claims 34-35.

39. The method of claim 38 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.

40. The method of claim 38 wherein the sphingosine-1-phosphate receptor subtype 1 is disposed within a living mammal.

41. 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 1-33 to the patient at a frequency and for a duration of time sufficient to provide a beneficial effect to the patient.

42. The method of claim 41 wherein selective activation or agonism of an S1P subtype 1 receptor with respect to other subtypes of S1P receptor is medically indicated.

43. The method of claim 41 or 42 wherein the malcondition comprises multiple sclerosis, transplant rejection, acute respiratory distress syndrome, ulcerative colitis, influenza, Crohn's disease or adult respiratory distress syndrome.

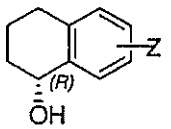
44. A method for the synthesis of a compound comprising a tetrahydronaphthalene moiety having a chiral carbon in the six-membered saturated ring of the tetrahydronaphthalene moiety where the compound is enantiomerically enriched with respect to the chiral carbon, the method comprising the steps of

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

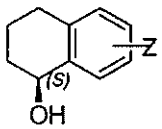
(ii) reacting such compound with a chiral reagent to form a chiral center at the tetrahydronaphthalene moiety carbon previously bound to the oxo group.

45. The method of claim 44 wherein the chiral reagent is RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN] or RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN].

46. The method of claims 44-45 wherein the compound comprising a tetrahydronaphthalene moiety provided in step (i) is contacted with the chiral reagent to form in step (ii) Formula **VI-R** or **VI-S**:



VI-R

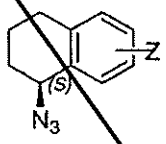


VI-S

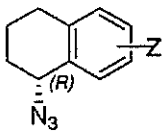
wherein Z is –CN, –Cl, or $–CF_3$.

47. The method of claim 46 wherein Z is –CN.

48. The method of claims 46 and 47 wherein the method further comprises the step of reversing the chiral configuration of the chiral carbon in the six-membered saturated ring of the tetrahydronaphthalene moiety that was previously bound to the oxo group by treating Formula **VI-R** or **VI-S** with diphenylphosphoryl azide (DPPA) to form an azido tetrahydronaphthalene of Formula **VII-S** or **VII-R**:



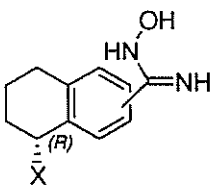
VII-S



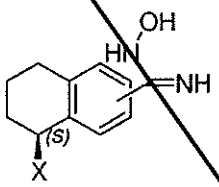
VII-R,

where the azido substituent in the six-membered saturated ring of the tetrahydronaphthalene moiety replacing the hydroxy substituent and the chiral carbon that is bound to the azido substituent has a reverse chiral configuration of the chiral carbon when it was previously bound to the hydroxy substituent .

49. The method of claim 48 wherein Z is –CN and the method further comprises the step of forming a substituted 1,2,4-oxadiazole on the tetrahydronaphthalene moiety by (a) reacting the intermediate of **VII-R** or **VII-S** with a protecting agent and then reacting the resulting protected form of the intermediate of **VII-R** or **VII-S** with a hydroxylamine or a hydroxylamine hydrochloride to form a hydroxyamidine at the phenyl carbon to which Z had been attached, the resulting compound of such reaction having the Formula **VIII-R** or **VIII-S**:

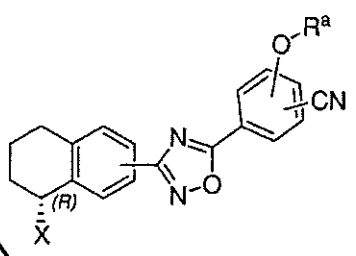


VIII-R

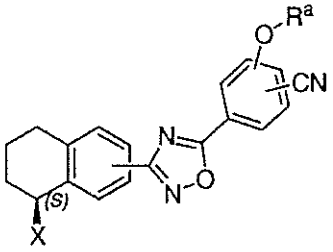


VIII-S; and

(b) contacting the intermediate of Formula **VIII-R** or **VIII-S** with substituted benzoic acid and a coupling reagent to form a compound of Formula **IX-R** or **XI-S**:



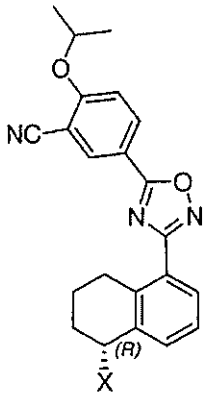
IX-R



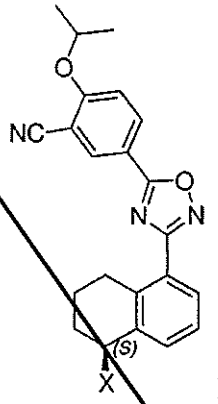
XI-S

wherein X is OH, N_3, NH-PG, NH_2 or NR'R"; PG is a protecting group; R' is H, C_{1-4} alkyl, n-hydroxy C_{1-4} alkyl, $-SO_2-R^1$, or $-CO-R^1$; R" is H, $-SO_2-R^3$, C_{1-4} alkyl optionally substituted with 1 or more R^2, or a ring moiety optionally substituted with R^4 wherein such ring moiety is piperidinyl, cyclohexyl, morpholinyl, thiazolyl, pyrazolyl, pyrrolidinyl, imidazolyl, or phenyl; R^a is lower alkyl and R^1, R^2, R^3, and R^4 are as defined in Claim 1.

50. The method of claim 49 wherein the compound of Formula **IX-R** or **IX-S** have the structures below:



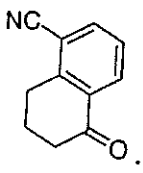
IX-R



XI-S.

51. The method of claims 49-50 wherein the coupling reagent is a mixture comprising hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC).

52. The method of claims 44-51 wherein the compound provided in step (i) is



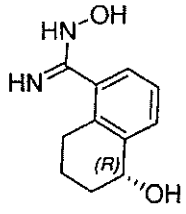
53. The method of claims 44-52 wherein the resulting compound comprising a tetrahydronaphthalene moiety having a chiral carbon in the six-membered saturated ring of the tetrahydronaphthalene moiety is enantiomerically enriched at least 90%.

54. The method of claim 53 wherein the resulting compound is enantiomerically enriched at least 95%.

55. The method of claim 54 wherein the resulting compound is enantiomerically enriched at least 98%.

56. The method of claim 55 wherein the resulting compound is enantiomerically enriched at least 99%.

57. A compound selected from the group consisting of:



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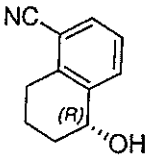

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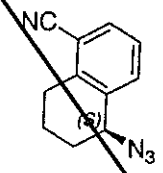

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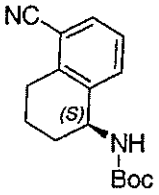

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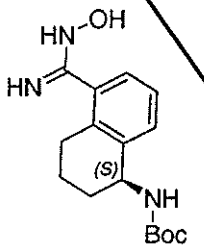

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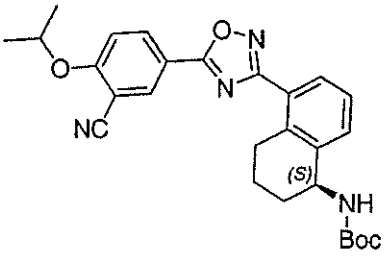

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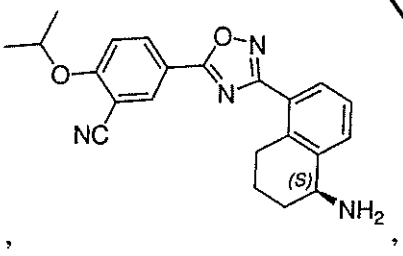

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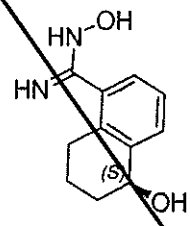
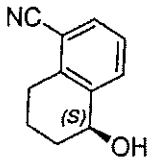
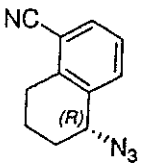
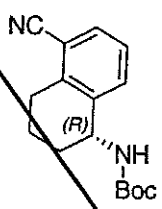
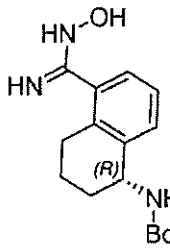
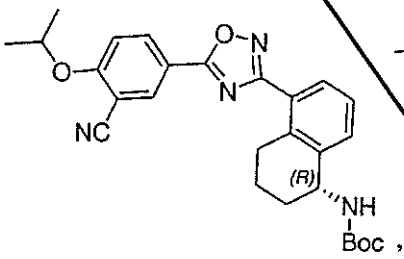
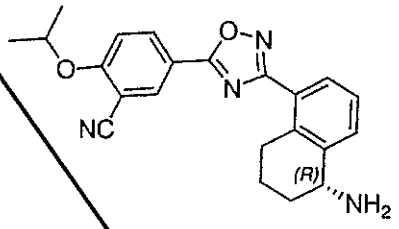
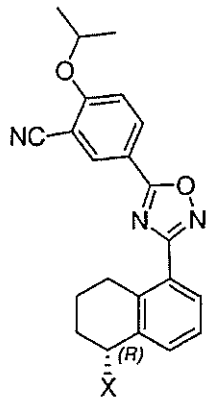



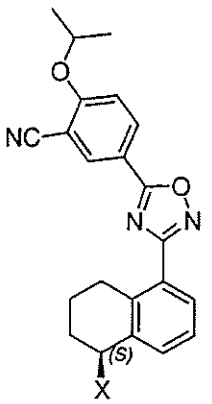






58. A method for the synthesis of a compound comprising a tetrahydronaphthalene moiety having a chiral carbon in the six-membered saturated ring of the tetrahydronaphthalene moiety where the compound is enantiomerically enriched with respect to the chiral carbon, the method comprising a step of providing a compound of claim 57.

59. The method of claim 58 wherein the compound comprising an indane moiety having a chiral carbon in the five-membered ring of the indane moiety is a compound of the Formula **IX-R** or **XI-S**:



IX-R



XI-S.

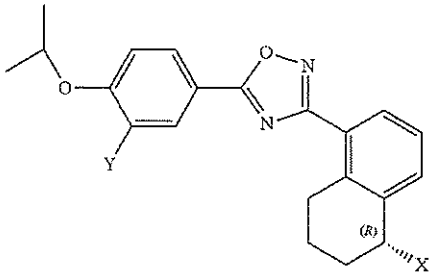
wherein X is as defined in claim 1.

60 The method of claim 59 wherein the compound of the Formula **IX-R** or **XI-S** is a compound of claims 1-33.

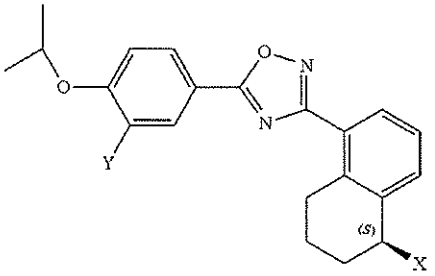
We claim:

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

I-R



I-S



wherein

X is —NR'R" or —OR'";

Y is —CN, —Cl, or —CF_3;

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

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

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

R'" is H, C_{1-4} alkyl, or —CO—R^1;

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

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

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

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

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

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

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

4. The compound of claim 1 wherein the compound is substantially enantiomerically pure.

5. The compound of claim 1 wherein Y is Cl.

6. The compound of claim 1 wherein Y is CF_3.

7. The compound of claim 1 wherein Y is CN.

8. The compound of claim 1 wherein X is —NR'R".

9. The compound of claim 1 wherein X is —OR'".

10. The compound of claim 9 wherein X is —OH.

11. The compound of claim 9 wherein X is —OCO—R^1.

12. The compound of claim 11 wherein R^1 is C_{1-3} alkyl.

13. The compound of claim 8 wherein R' is H.

14. The compound of claim 8 wherein R' is —COR^1.

15. The compound of claim 8 wherein R' is —SO_2—R^1.

16. The compound of claim 8 wherein R" is H.

17. The compound of claim 8 wherein R" is —SO_2—R^3.

18. The compound of claim 8 wherein R" is C_{1-4} alkyl optionally substituted with 1 or more R^2.

19. The compound of claim 8 wherein R" is —$(CR^aR^b)_n$-R^2; each R^a and each R^b is independently selected from the group consisting of H, hydroxyl and methyl or R^a and R^b bound to the same carbon taken together are oxo; and n is 0, 1, 2, or 3.

20. The compound of claim 19 wherein n is 2.

21. The compound of claim 20 wherein R^2 is —OH, —NH_2, —NHR^1, —$N(R^5R^5)$, or —COOH.

22. The compound of claim 17 wherein R^3 is $C_{1\text{-}4}$ alkyl optionally substituted with 1 or more R^2.

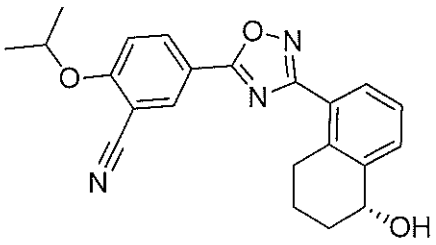
23. The compound of claim 17 wherein Y is CN.

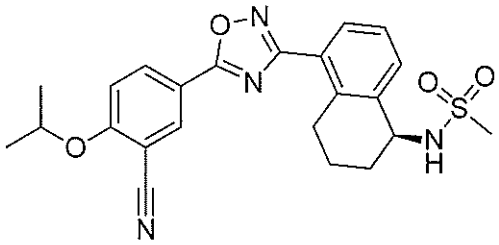
24. The compound of claim 22 wherein R^3 is —C_2H_5—$N((R^5R^5)$ or —CH_2—CO—$N(R^5R^5)$.

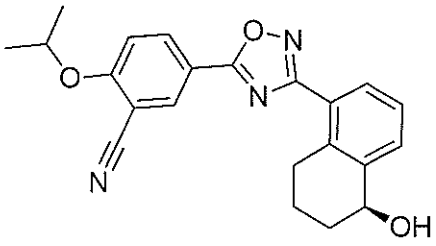
25. The compound of claim 23 wherein R^3 is C_2H_5—O—R^1.

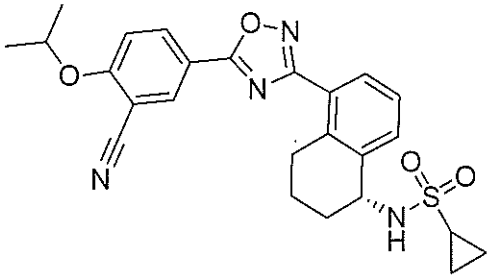
26. The compound of claim 7 wherein X is —NH—CO—$N(R^5R^5)$.

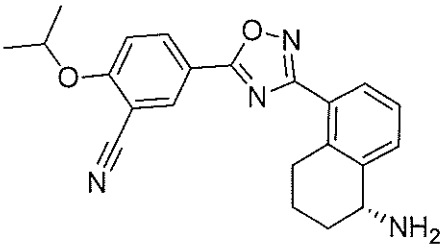
27. The compound of claim 1 wherein the compound is selected from the group consisting of:

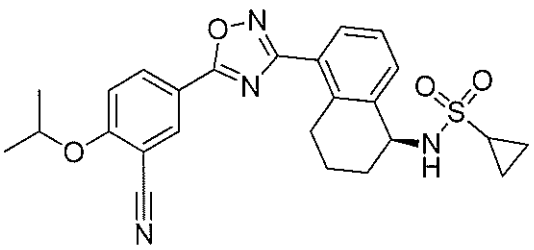


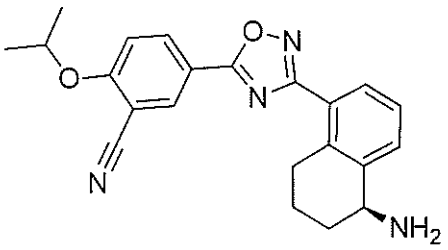


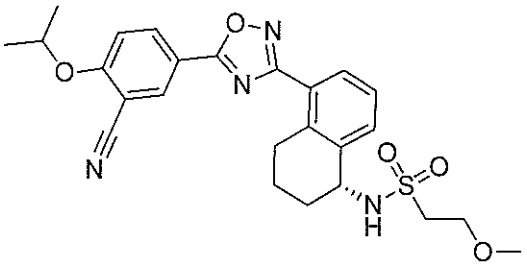


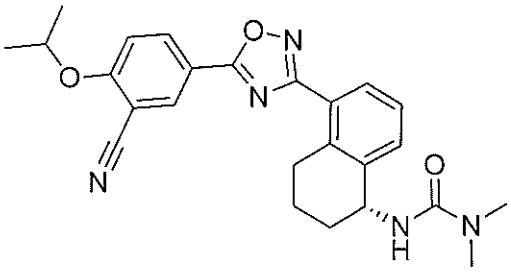


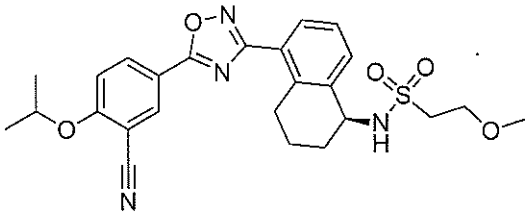


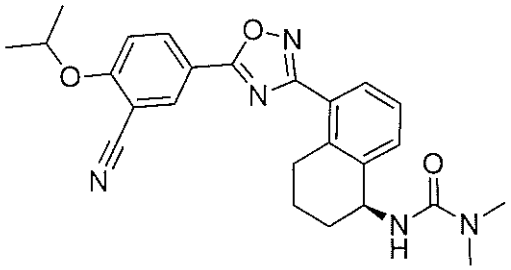


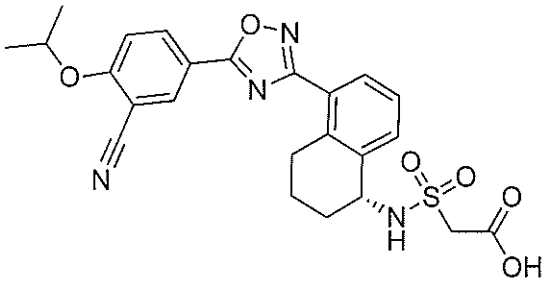


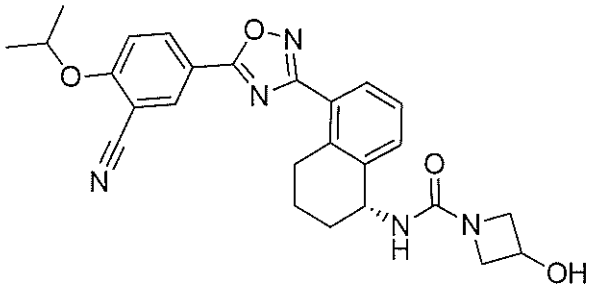


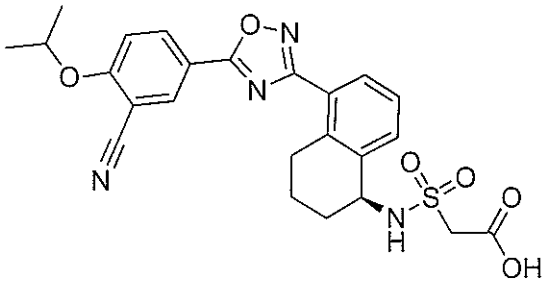


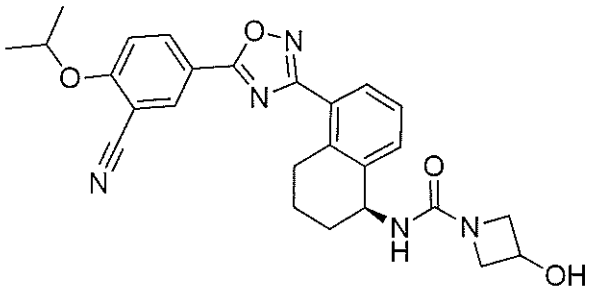


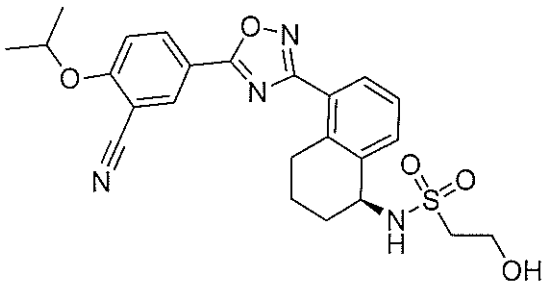


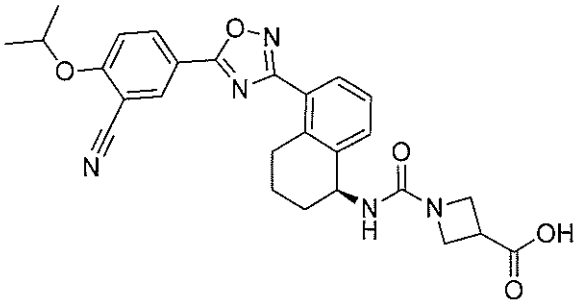


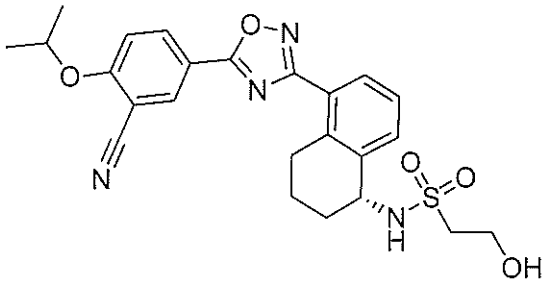


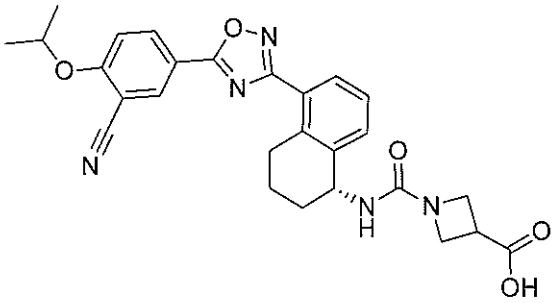


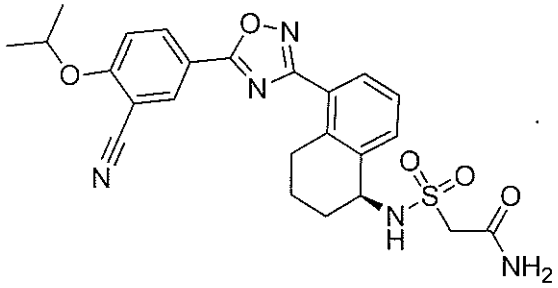


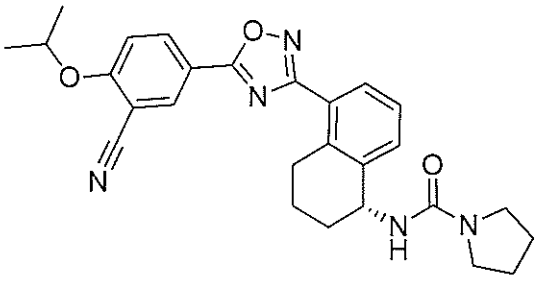


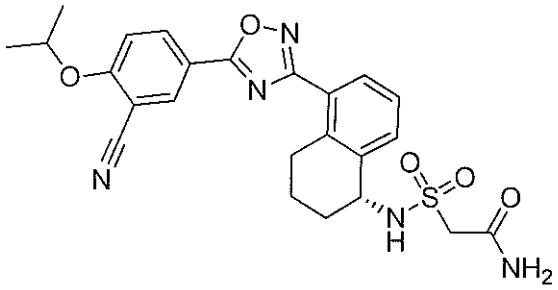


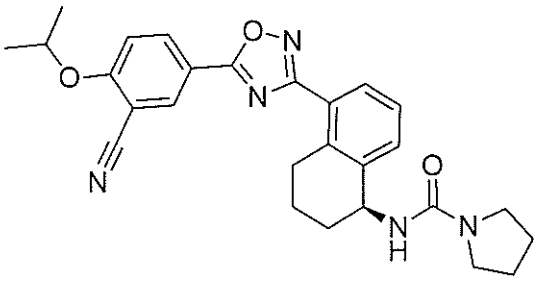


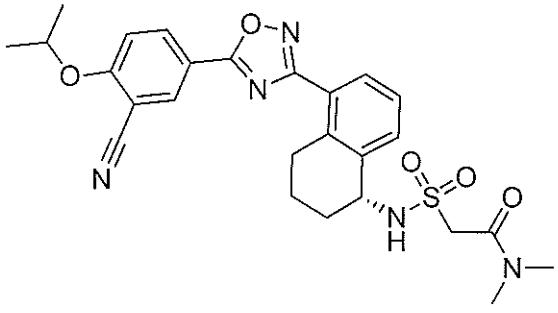


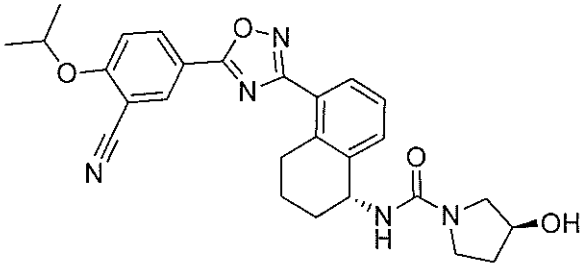


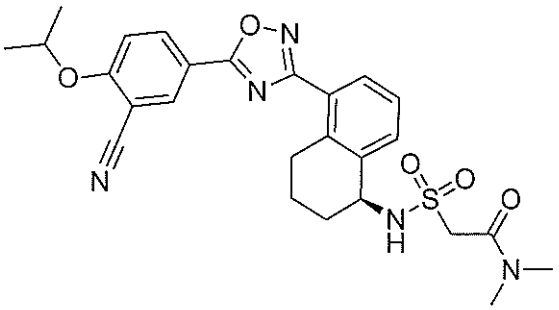


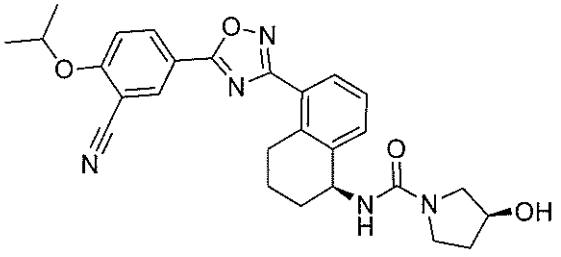


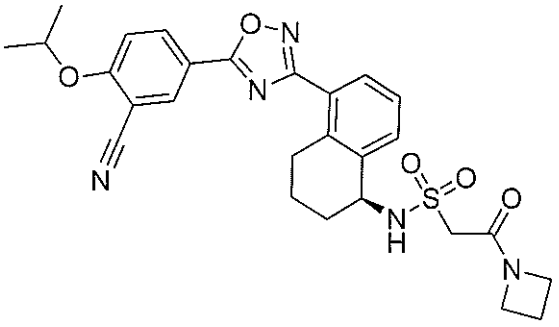


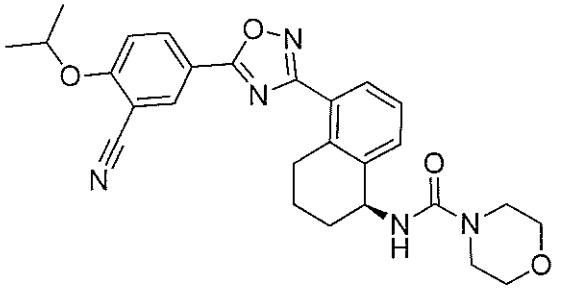


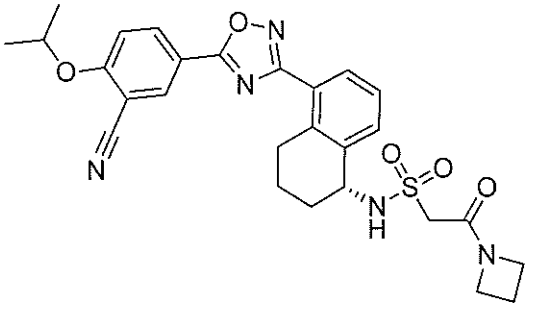


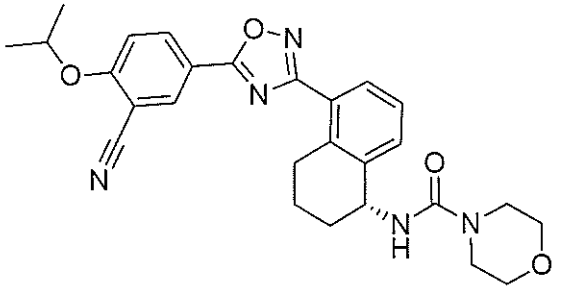


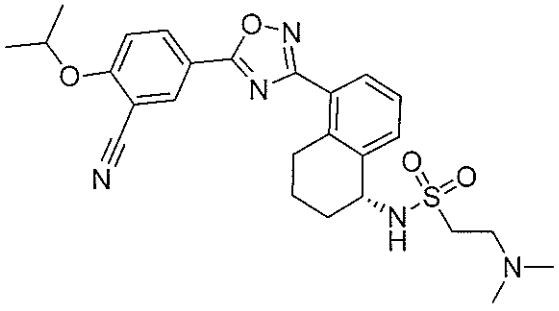


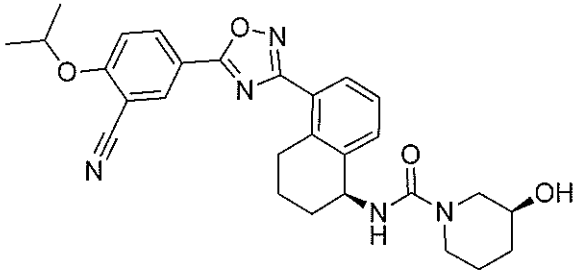


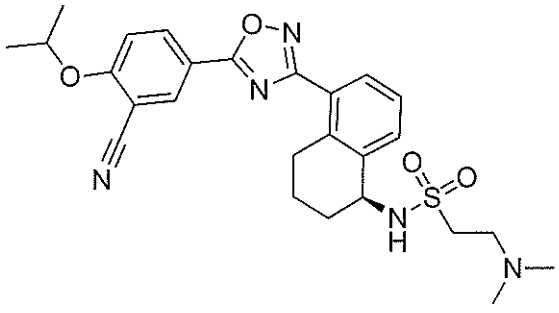


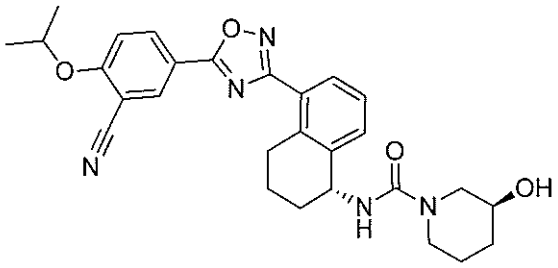


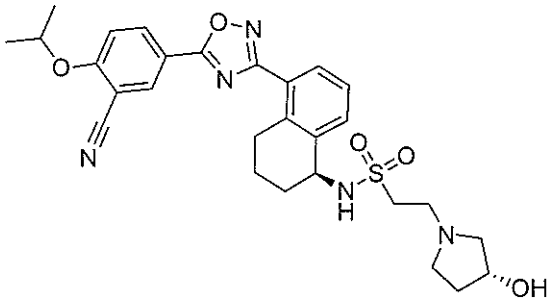


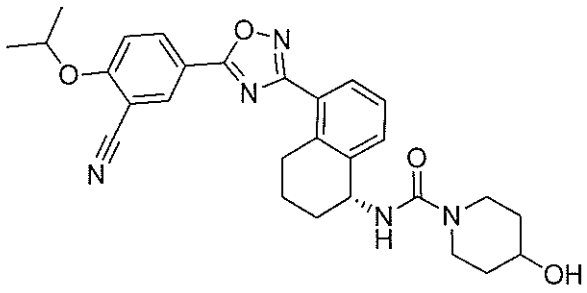


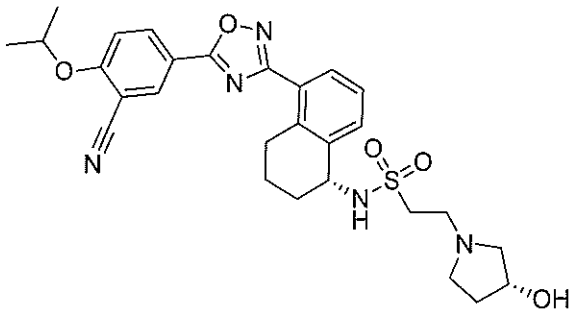


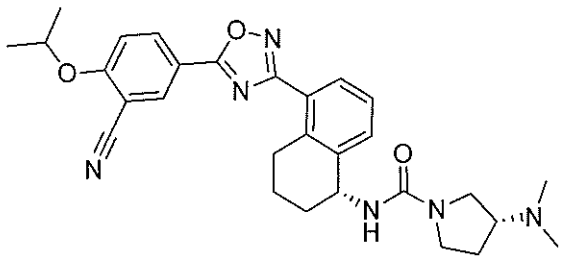


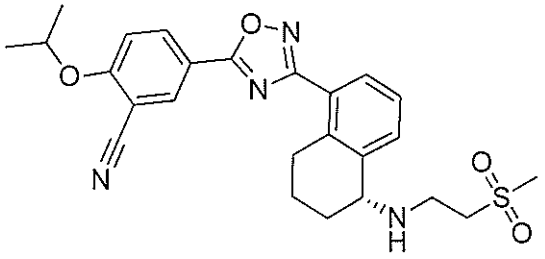


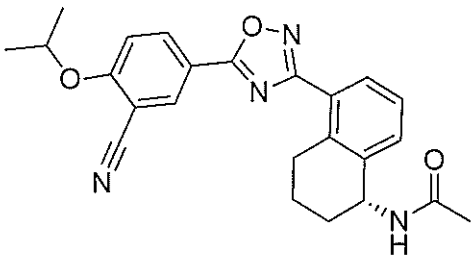


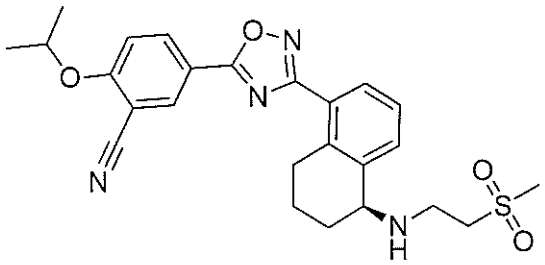


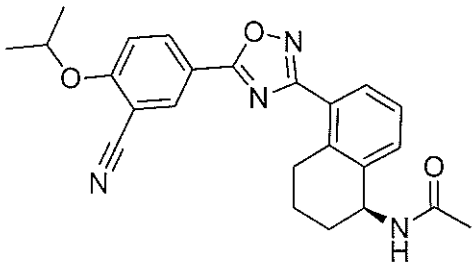


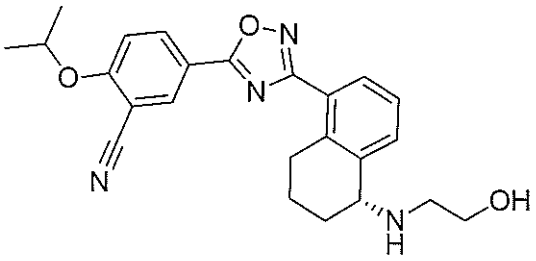


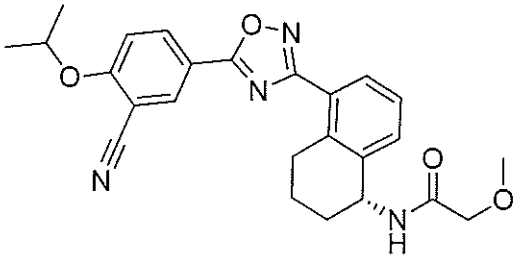


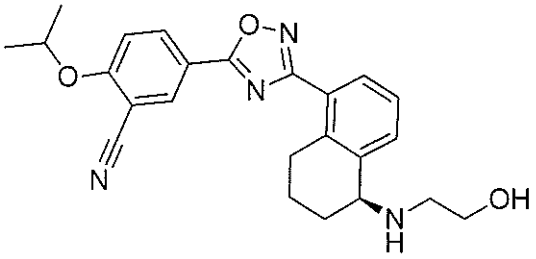


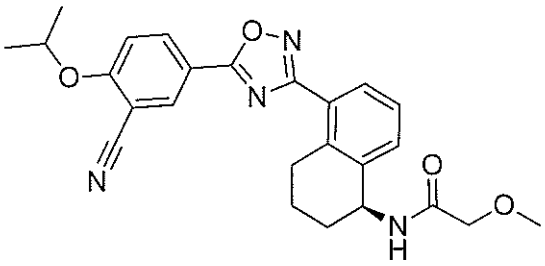


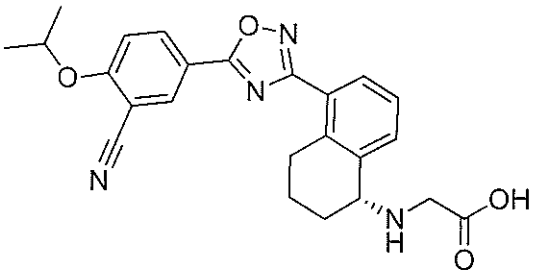


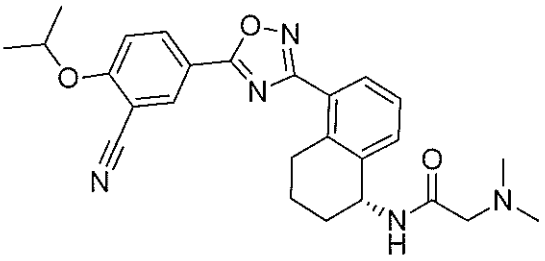


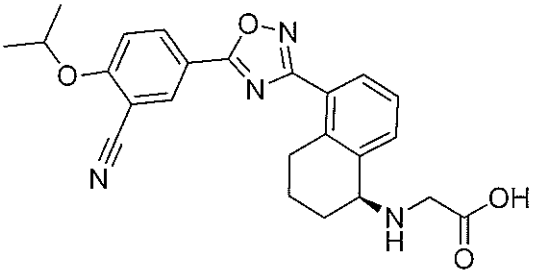


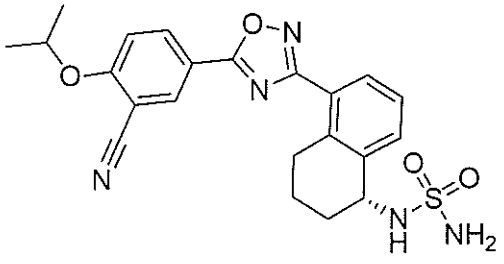


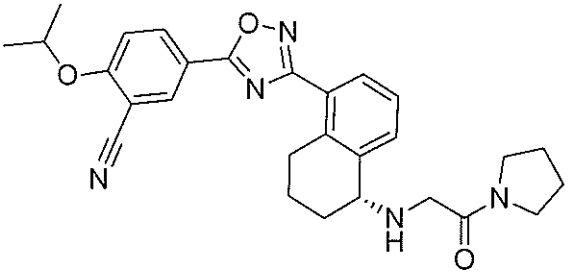


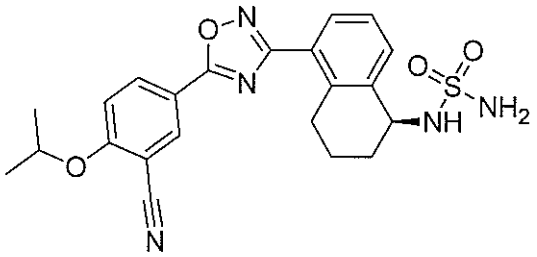


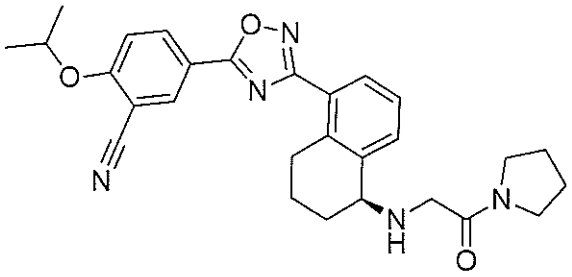


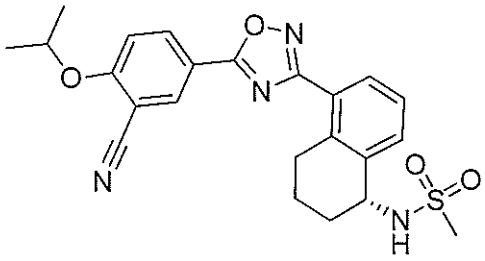








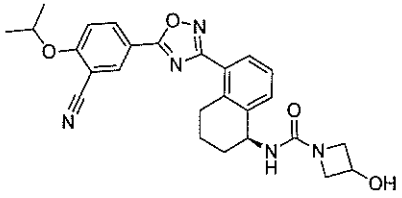


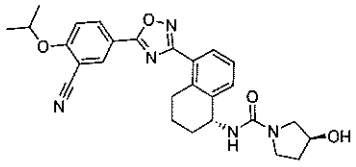


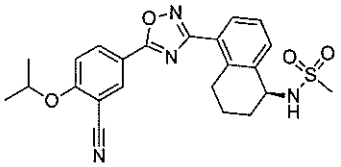
and

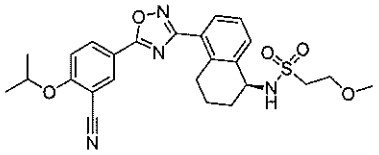
or a pharmaceutically acceptable salt, ester, hydrate or solvate thereof.

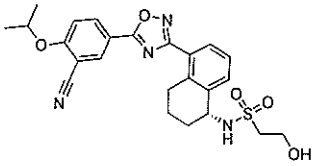
28. The compound of claim 27 selected from the group consisting of:



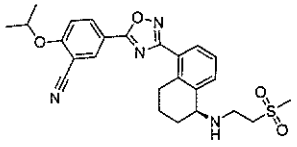








and



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

29. A pharmaceutical composition comprising a compound of claims 1-4 and 5-28 and a suitable excipient.

30. A pharmaceutical combination comprising the compound of claims 1-4 and 5-28 and a second medicament.

31. The combination of claim 30 wherein the second medicament is medically indicated for the treatment of multiple sclerosis, transplant rejection, or acute respiratory distress syndrome.