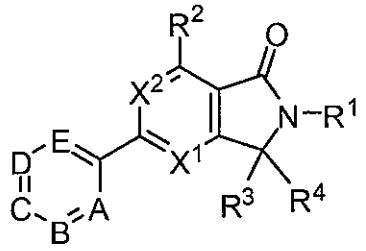
CLAIMS

What is claimed is:

1. A compound having the formula:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is N or CH;

$X^2$ is N, CH, or C-$CH_3$;

$R^1$ is selected from a phenyl ring, a 5-6 membered heteroaryl ring, a pyridone ring, or a 9-10 membered fused bicyclic heteroaryl or heterocyclic ring system wherein each of said rings or ring systems is optionally substituted with 1 or 2 independent occurrences of $R^{1a}$ and each of said heteroaryl or heterocyclic rings has 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, or sulfur;

$R^{1a}$ is chloro, fluoro, $C_{1-8}$aliphatic, $-(CH_2)_{0-2}C_{3-6}$cycloaliphatic, $-(CH_2)_{0-2}$-5-6 membered heterocyclic having up to two heteroatoms selected from nitrogen, oxygen, or sulfur, -CN, $-C(O)C_{1-4}$aliphatic, $-C(O)NH(C_{1-4}$aliphatic), $-C(O)N(C_{1-4}$aliphatic$)_2$, $-C(O)OC_{1-4}$aliphatic, $-S(O)_2NH(C_{1-4}$aliphatic), $-S(O)_2N(C_{1-4}$aliphatic$)_2$, or $-S(O)_2C_{1-4}$aliphatic, wherein up to 3 non-adjacent carbon atoms of said aliphatic or cycloaliphatic of $R^{1a}$ can be substituted for by -O-, -S-, or $-N(R^{1b})$- and wherein each of said aliphatic, cycloaliphatic, or heterocyclic of $R^{1a}$ is optionally and independently substituted with up to 4 occurrences of $J^R$;

each $J^R$ is independently fluoro, oxo, $-(CH_2)_{0-2}CN$, $-(CH_2)_{0-2}CF_3$, $-C(O)R^{1b}$, $-C(O)N(R^{1b})_2$, $-C(O)O(R^{1b})$, $-N(R^{1b})_2$, $-N(R^{1b})C(O)R^{1b}$, $-(CH_2)_{0-2}OR^{1b}$, phenyl, or a 5-6 membered heteroaryl, 4-6 heterocyclyl, or 9-11 fused bicyclic heteroaryl or heterocyclyl, each of said heteroaryl or heterocyclyl rings having up to 3 atoms selected from nitrogen, oxygen, or

sulfur, wherein each of said cycloaliphatic, phenyl, heteroaryl, or heterocyclyl is optionally substituted with up to 2 $R^{1c}$;

each $R^{1b}$ is, independently, selected from hydrogen, $C_{1-8}$aliphatic, $-(CH_2)_{0-1}C_{3-6}$cycloaliphatic, $-(CH_2)_{0-1}C_{4-6}$heterocyclic having up to two heteroatoms selected from N or O, or two $R^{1b}$ together with the atom to which they are bonded form a 5-6 membered heterocyclic ring, wherein each aliphatic, cycloaliphatic, or heterocyclic is optionally substituted with up to three F atoms or up to two -OH, $-C_{1-2}$alkyl, or $-OC_{1-2}$alkyl groups;

each $R^{1c}$ is, independently, fluoro, chloro, $C_{1-4}$aliphatic, $-(CH_2)_{0-2}OH$, -CN, $-C(O)C_{1-4}$aliphatic, or $-C(O)OC_{1-4}$aliphatic;

$R^2$ is hydrogen, F, Cl, $CF_3$, $C_{1-2}$aliphatic, $C_{3-4}$cycloaliphatic, $-N(CH_3)_2$, $-N(CH_2)_3$, $-OCF_3$, $-OCHF_2$, or $-OC_{1-2}$aliphatic;

$R^3$ is hydrogen, $C_{1-6}$aliphatic, $C_{3-6}$ cycloaliphatic, $C_{4-7}$heterocyclyl having 1 or 2 atoms selected from N or O, $-(CH_2)_{0-1}CF_3$, -OH, $-OC_{1-6}$aliphatic, $-OC_{3-6}$cycloaliphatic, $-OC_{3-6}$heterocyclyl having one oxygen atom, $-O(CH_2)_2OC_{1-2}$aliphatic, or $-OC_{1-2}$alkylC(O)$OC_{1-3}$aliphatic, or benzyl; and

$R^4$ is hydrogen or $C_{1-6}$alkyl; or $R^3$ and $R^4$ together with the carbon to which they are bonded form a 3-6 membered cycloaliphatic ring, a 3-6 membered heterocyclic ring having up to two atoms selected from N or O, or a $C_2$alkenyl, wherein each of said aliphatic, cycloaliphatic, or heterocyclyl of $R^3$, $R^4$, or $R^3$ and $R^4$ together is optionally substituted with up to three F atoms, or up to two $C_{1-2}$alkyl, $-C(O)C_{1-4}$alkyl, $-C(O)OC_{1-4}$alkyl, -OH, or $-OC_{1-2}$alkyl groups;

A is N or $CR^A$;

B is N or $CR^B$, or A=B is a sulfur atom;

C is N or $CR^C$;

D is N or $CR^D$;

E is N or $CR^E$ wherein no more than two of A, B, C, D, or E is N;

$R^A$ is hydrogen, $CH_3$, or $OCH_3$;

$R^B$ is hydrogen, F, Cl, $C_{1-3}$aliphatic, $-(CH_2)_{0-1}CF_3$, $-(CH_2)_{0-1}CHF_2$, or $-O(CH_2)_{0-1}CF_3$;

$R^C$ is hydrogen, F, Cl, $C_{1-3}$aliphatic, $-(CH_2)_{0-1}CF_3$, $-(CH_2)_{0-1}CHF_2$, $N(R^{1b})_2$, -OH, $-O(CH_2)_{0-1}CF_3$, or $-OC_{1-8}$aliphatic, wherein up to 2 non-adjacent carbon atoms of said aliphatic can be substituted for by -O-;

$R^D$ is hydrogen, fluoro, chloro, $C_{1-4}$aliphatic, -C(O)OH, $-C(O)OC_{1-4}$aliphatic, $-C(O)N(R^{1b})_2$, -CN, $-C(R^{D1})$=N-$OR^{1b}$, $-N(R^{1b})_2$, $-N(R^{D1})C(O)C_{1-4}$aliphatic, $-N(R^{D1})C(O)$phenyl, $-N(R^{D1})S(O)_2C_{1-4}$aliphatic, $-N(R^{D1})S(O)_2N(R^{1b})_2$, $-N(R^{D1})S(O)_2$phenyl -OH, $-OC_{1-8}$aliphatic, $-O(CH_2)_{0-1}C_{3-6}$cycloaliphatic, $-SC_{1-4}$aliphatic, $-S(O)C_{1-4}$aliphatic, $-S(O)_2C_{1-4}$aliphatic, or $-S(O)_2N(R^{1b})_2$; wherein up to 2 non-adjacent carbon atoms of said aliphatic, cycloaliphatic, or heterocyclic of $R^D$ can be substituted for by -O- and each of said aliphatic, cycloaliphatic, or phenyl of $R^D$ can be substituted with up to 5 fluorine atoms; or $R^D$ and $R^C$ together with the atoms to which they are attached form a phenyl or pyridyl ring;

each $R^{D1}$ is, independently, hydrogen or $C_{1-2}$alkyl; and

$R^E$ is hydrogen, F, Cl, $-NHC(O)C_{1-8}$aliphatic, -OH, $-OC_{1-2}$aliphatic, $-(CH_2)_{0-1}CF_3$, $-(CH_2)_{0-1}CHF_2$, $C_{1-3}$aliphatic, $C_{3-4}$cycloaliphatic, $N(R^{1b})_2$, azetidin-1-yl.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

$R^D$ is hydrogen, fluoro, chloro, $C_{1-4}$aliphatic, $-(CH_2)_{0-1}CF_3$, $-C(O)N(R^{1b})_2$, -CN, $-N(R^{1b})_2$, $-NHC(O)C_{1-8}$aliphatic, -OH, $-O(CH_2)_{0-1}CF_3$, $-O(CH_2)_{0-1}CHF_2$, $-O(CH_2)_{0-1}CH_2F$, $-OC_{1-8}$aliphatic, $-O(CH_2)_{0-1}C_{3-6}$cycloaliphatic, $-SC_{1-8}$aliphatic, $-S(O)_2C_{1-8}$aliphatic, $-S(O)_2N(R^{1b})_2$; wherein up to 2 non-adjacent carbon atoms of said aliphatic, cycloaliphatic, or heterocyclic of $R^D$ can be substituted for by -O-, or $R^D$ and $R^C$ together with the atoms to which they are attached form a phenyl or pyridyl ring;

$R^3$ is hydrogen, $C_{1-6}$alkyl, $C_{3-6}$ cycloalkyl, $-(CH_2)_{0-1}CF_3$, -OH, $-OC_{1-6}$alkyl, $-OC_{3-6}$cycloalkyl, $-OC_{3-6}$heterocyclyl having one oxygen atom, $-O(CH_2)_2OC_{1-2}$alkyl, or $-OC_{1-2}$alkyl$C(O)OC_{1-3}$alkyl, or benzyl; and

$R^4$ is hydrogen or $C_{1-6}$alkyl; or $R^3$ and $R^4$ together with the carbon to which they are bonded form a 3-6 membered cycloalkyl ring, a 3-6 membered heterocyclic ring having one

oxygen atom, wherein each of said alkyl, cycloalkyl, or heterocyclyl of $R^3$, $R^4$ or $R^3$ and $R^4$ together is optionally substituted with up to two F, $C_{1-2}$alkyl or -$OC_{1-2}$alkyl.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

each $R^{1b}$ is, independently, selected from hydrogen, $C_{1-4}$aliphatic, or $C_{3-6}$cycloaliphatic;

$R^B$ is hydrogen, F, Cl, -$OCF_3$, -$OC_{1-2}$aliphatic, -$CF_3$, or $C_{1-2}$aliphatic;

$R^C$ is hydrogen, F, Cl, $C_{1-3}$aliphatic, -$(CH_2)_{0-1}CF_3$, -$N(R^{1b})_2$, -OH, -$OCF_3$, or -$OC_{1-8}$aliphatic;

$R^D$ is hydrogen, fluoro, chloro, $C_{1-4}$aliphatic, $(CH_2)_{0-1}CF_3$, -$C(O)NHC_{1-8}$aliphatic, -CN, -$N(R^{1b})_2$, -$NHC(O)C_{1-8}$aliphatic, -OH, -$OCF_3$, -$OCHF_2$, -$OC_{1-8}$aliphatic, -$O(CH_2)_{0-1}C_{3-6}$cycloaliphatic, -$SC_{1-8}$aliphatic, -$S(O)_2C_{1-8}$aliphatic, -$S(O)_2N(R^{1b})_2$; wherein up to 2 non-adjacent carbon atoms of said aliphatic or cycloaliphatic of $R^D$ can be substituted for by -O-, or $R^D$ and $R^C$ together with the atoms to which they are attached form a phenyl or pyridyl ring;

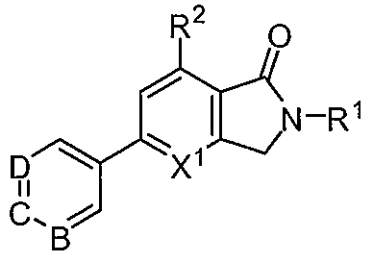
$R^E$ is hydrogen, F, Cl, -$NHC(O)C_{1-8}$aliphatic, -OH, -$OCF_3$, -$OC_{1-2}$aliphatic, $CF_3$, $C_{1-2}$aliphatic, $C_{3-4}$cycloaliphatic, $N(CH_3)_2$, azetidin-1-yl;

$R^2$ is hydrogen, F, Cl, $CF_3$, $C_{1-2}$aliphatic, $C_{3-4}$cycloaliphatic, -$N(CH_3)_2$, -$N(CH_2)_3$, -$OCF_3$, or -$OC_{1-2}$aliphatic; and

$R^3$ is hydrogen, $C_{1-2}$alkyl, -OH, -$OC_{1-2}$alkyl, -$O(CH_2)_2OC_{1-2}$alkyl, or -$OC_{1-2}$alkyl$C(O)OC_{1-2}$alkyl; and

$R^4$ is hydrogen or $C_{1-2}$alkyl.

4. The compound according to claim 1 having the formula:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is CH or N;

$R^1$ is selected from a phenyl ring, a 5-membered heteroaryl ring, a 6-membered heteroaryl ring, or a 9- or 10-membered fused bicyclic heteroaryl or heterocyclic ring system wherein each of said rings or ring systems is optionally substituted with 1 or 2 independent occurrences of $R^{1a}$ and each of said heteroaryl or heterocyclic rings has 1, 2, or 3 heteroatoms selected from nitrogen, oxygen, or sulfur;

$R^{1a}$ is chloro, fluoro, $C_{1-6}$aliphatic, $C_{3-6}$cycloaliphatic, -CN, $-C(O)R^{1b}$, $-C(O)N(R^{1b})_2$, $-C(O)O(R^{1b})$, or $-OR^{1b}$, wherein each of said aliphatic or cycloaliphatic is optionally substituted with up to 3 occurrences of $J^R$;

each $J^R$ is independently fluoro, oxo, -CN, $-C(O)R^{1b}$, $-C(O)N(R^{1b})_2$, $-C(O)O(R^{1b})$, $-N(R^{1b})_2$, $-N(R^{1b})C(O)R^{1b}$, $-OR^{1b}$, or a 5-membered heteroaryl or heterocyclyl having up to 3 atoms selected from nitrogen, oxygen, or sulfur;

each $R^{1b}$ is independently selected from hydrogen, $C_{1-4}$ aliphatic, or $C_{3-6}$ cycloaliphatic;

$R^2$ is hydrogen, F, Cl, $CF_3$, or $CH_3$;

B is N;

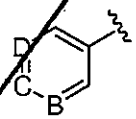
C is $CR^C$, wherein $R^C$ is hydrogen, fluoro, chloro, $C_{1-3}$aliphatic, $CF_3$, $-OCF_3$, or $-OC_{1-2}$aliphatic; and

D is $CR^D$, wherein $R^D$ is fluoro, chloro, $C_{1-3}$aliphatic, $CF_3$, $-OCF_3$, or $-OC_{1-2}$aliphatic.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein $X^1$ is N.

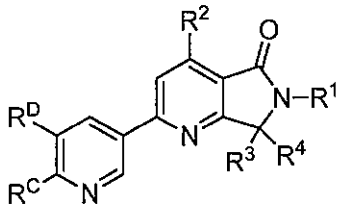
6. The compound according to to claim 5, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is $CH_3$.

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein




is a substituted pyridine-3-yl.

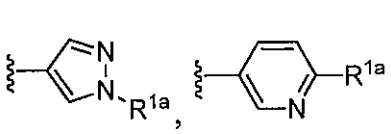
8. The compound according to claim 1 having the formula:

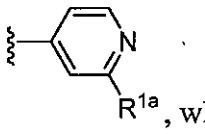


**(I-A),**

or a pharmaceutically acceptable salt thereof, wherein

$R^1$ is



, or , wherein

$R^{1a}$ is -$C_{1-4}$alkyl, optionally and independently substituted with -CN, up to three F atoms, or up to two $CH_3$, -$OC_{1-2}$alkyl, or -OH groups;

$R^2$ is $C_{1-2}$alkyl;

$R^3$ is hydrogen, -OH, -$OC_{1-4}$ alkyl, or $C_{1-4}$alkyl optionally substituted with up to two -OH groups;

$R^4$ is hydrogen or $CH_3$, or $R^3$ and $R^4$ together form a $C_{3-6}$cycloalkyl ring optionally substituted with up to two OH groups, or a 4-6 membered heterocyclic ring having one oxygen or anitrogen atom optionally substituted with $C_{1-4}$alkyl, -$C(O)C_{1-4}$alkyl, or $C(O)O$ $C_{1-4}$alkyl;

$R^C$ is hydrogen, F, $C_{1-2}$alkyl, or -$OC_{1-2}$alkyl; and

$R^D$ is -$OR^{D1}$, -$C(O)N(R^{D1})R^{D2}$, -$S(O)_2N(R^{D1})R^{D2}$, -$S(O)_{1-2}R^{D2}$, -$N(R^{D1})S(O)_2R^{D2}$, or -$N(R^{D1})S(O)_2N(R^{D1})R^{D2}$, wherein

$R^{D1}$ is hydrogen or $C_{1-2}$alkyl, and $R^{D2}$ is $C_{1-4}$alkyl, -$(CH_2)_{0-1}C_{3-6}$cycloalkyl, or -$(CH_2)_{0-1}C_{4-6}$heterocyclyl having up to two oxygen or nitrogen atoms, each alkyl, cycloalkyl, or heterocyclyl optionally substituted with up to three F atoms or up to two -OH groups.

9. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^{1a}$ is $C_{1-2}$alkyl, optionally substituted with up to 3 fluorine atoms.

10. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^{1a}$ is $C_{1-4}$alkyl, optionally substituted with CN.

11. The compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is $CH_3$.

12. The compound according to claim 8, or a pharmaceutical acceptable salt thereof, wherein at least one of $R^3$ and $R^4$ is not hydrogen.

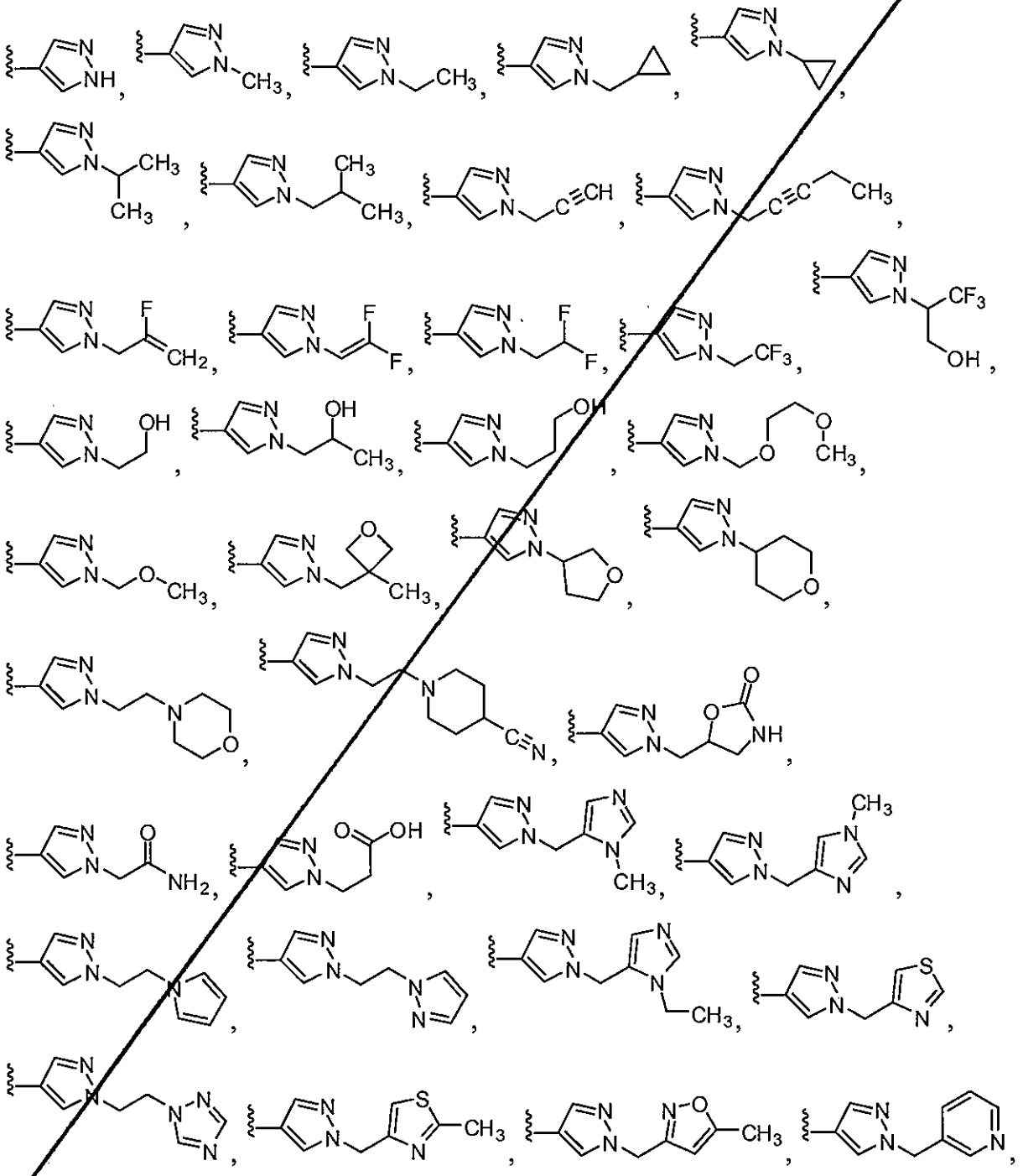
13. The compound according to claim 12, or a pharmaceutical acceptable salt thereof, wherein each of $R^3$ and $R^4$ is $CH_3$.

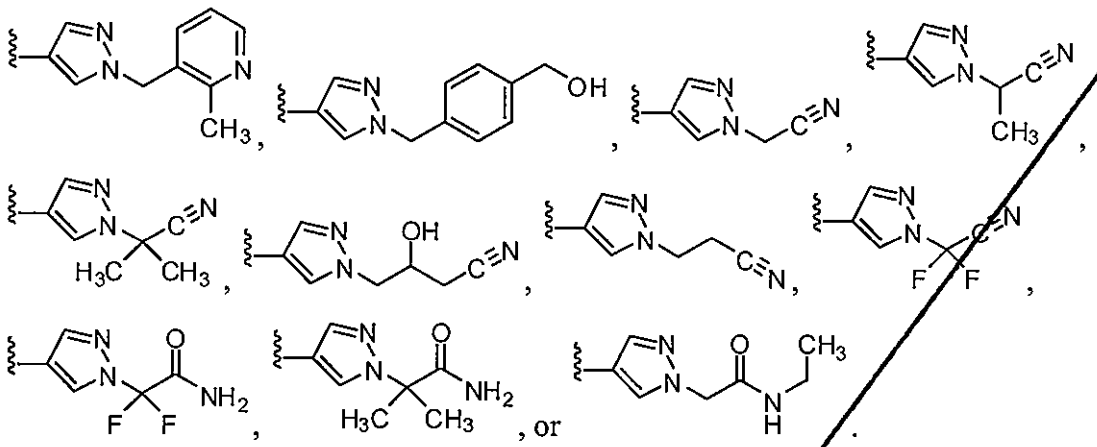
14. The compound according to claim 12, or a pharmaceutical acceptable salt thereof, wherein $R^3$ and $R^4$ together form a 4-6 membered heterocyclic ring having one oxygen or a nitrogen atom optionally substituted with $C_{1-4}$alkyl, $-C(O)C_{1-4}$alkyl, or $-C(O)OC_{1-4}$alkyl.

15. The compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is a 5-membered heteroaryl ring having 1-3 heteroatoms selected from N, O, or S and optionally substituted with 1 or 2 $R^{1a}$ groups.

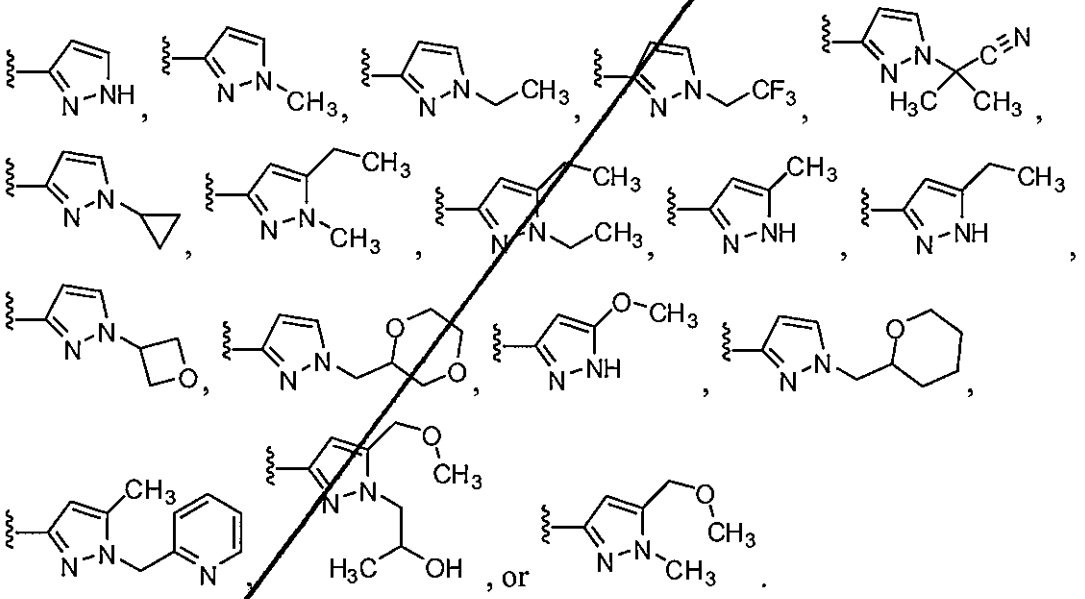
16. The compound according to claim 15, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is an optionally substituted pyrazol-4-yl, pyrazol-3-yl, imidazol-4-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, 1,2,5-triazol-3-yl, 1,3-thiazol-4-yl, 1,3-thiazol-2-yl, 1,2-thiazol-5-yl, 1,2-isoxazol-3-yl.

17. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is selected from

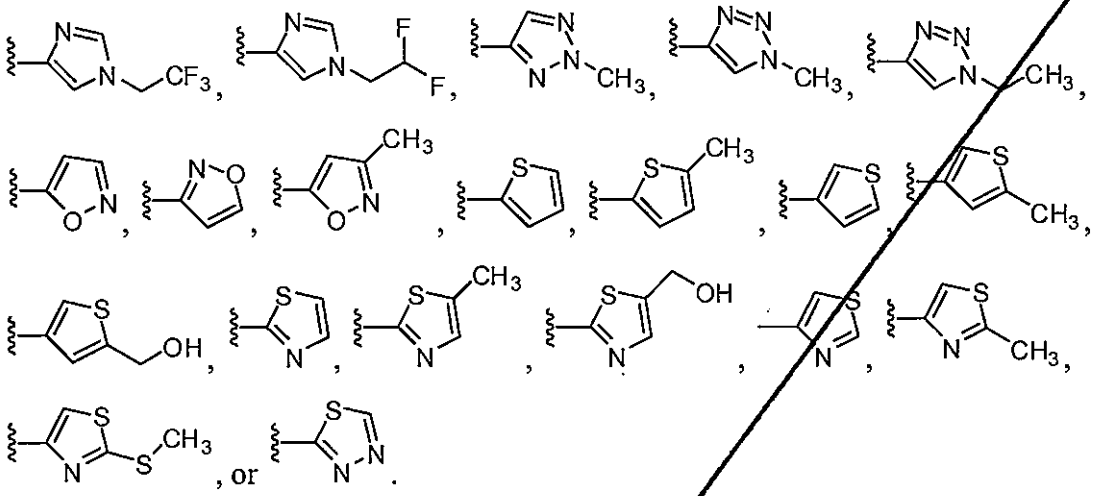




18. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is selected from

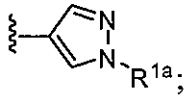


19. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is selected from



20. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is



$R^2$ is $CH_3$;

$R^3$ is hydrogen, $C_{1-2}$alkyl, OH, or $OCH_3$;

$R^4$ is hydrogen or $CH_3$;

$R^C$ is hydrogen; and

$R^D$ is -$OC_{1-2}$alkyl or -$OC_{3-5}$cycloalkyl, each optionally substituted with up to 3 fluorine atoms.

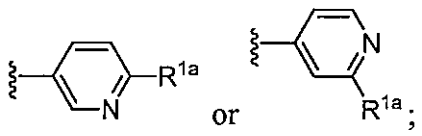
21. The compound according to claim 20, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is 1-(2,2-difluoroethyl)-1*H*-pyrazol-4-yl or 1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl.

22. The compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is a 6-membered heteroaryl ring having 1-3 nitrogens and optionally substituted with 1 or 2 $R^{1a}$ groups.

23. The compound according to claim 22, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is an optionally substituted pyridinyl group.

24. The compound according to claim 23, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is



$R^2$ is $CH_3$;

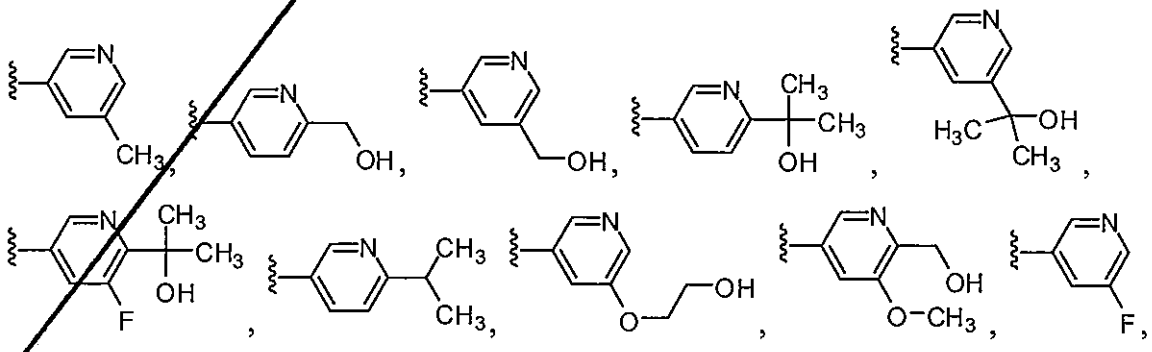
$R^3$ is hydrogen, $C_{1-2}$alkyl, OH, or $OCH_3$;

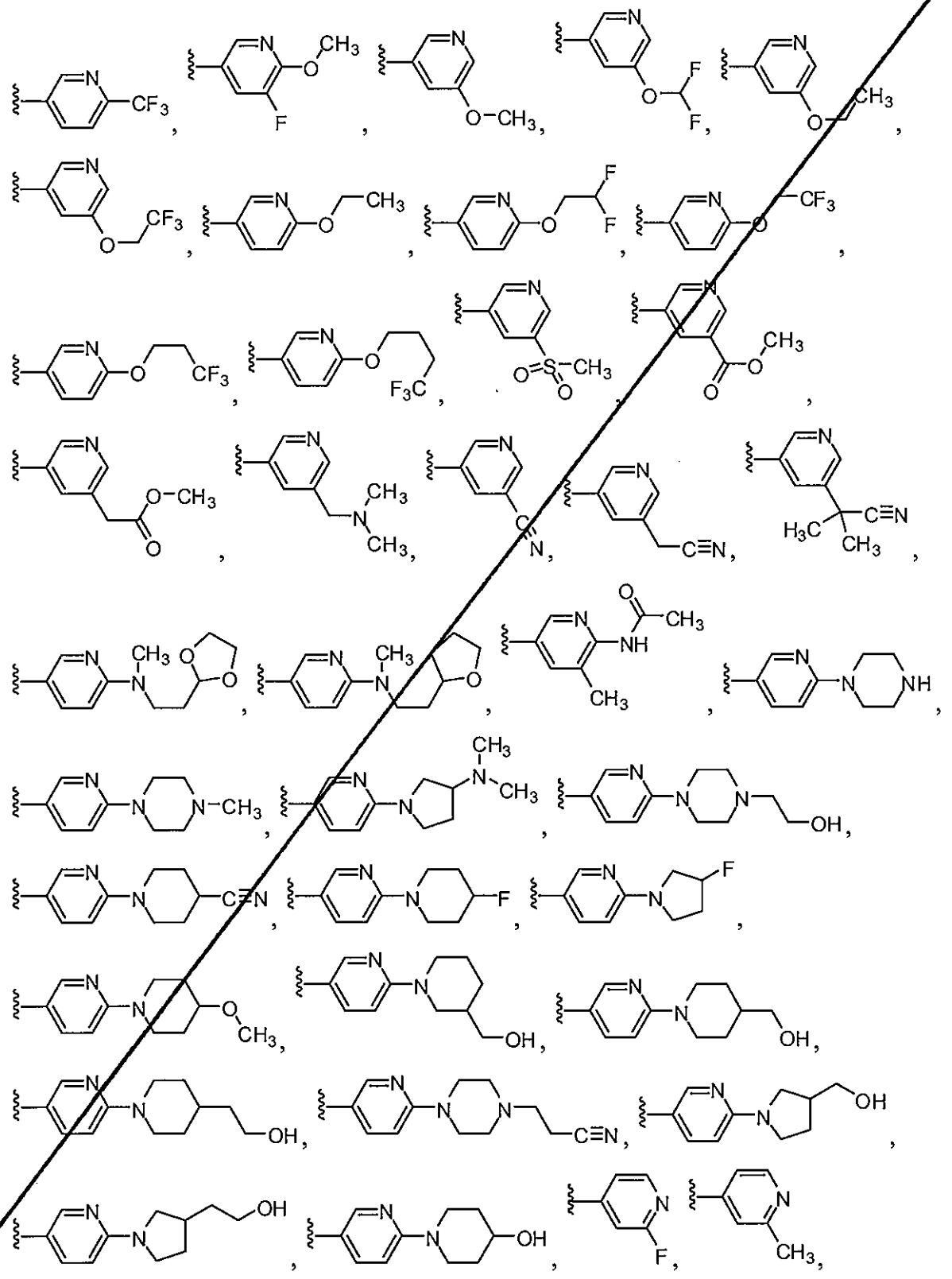
$R^4$ is hydrogen or $CH_3$;

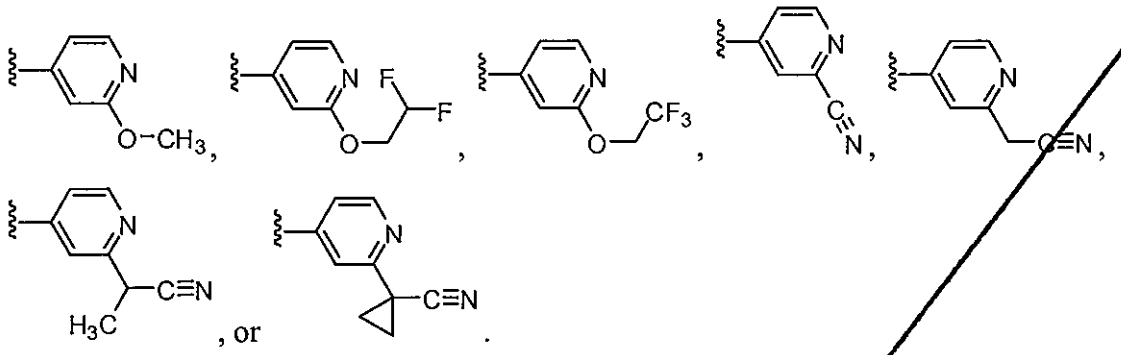
$R^C$ is hydrogen, F, Cl, $C_{1-3}$aliphatic, $(CH_2)_{0-1}CF_3$, $-OCF_3$, or $-OC_{1-8}$aliphatic; and

$R^D$ is $-C(O)NHC_{1-8}$aliphatic.

25. The compound according to claim 24, or a pharmaceutical acceptable salt thereof, wherein $R^1$ is selected from





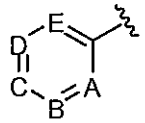


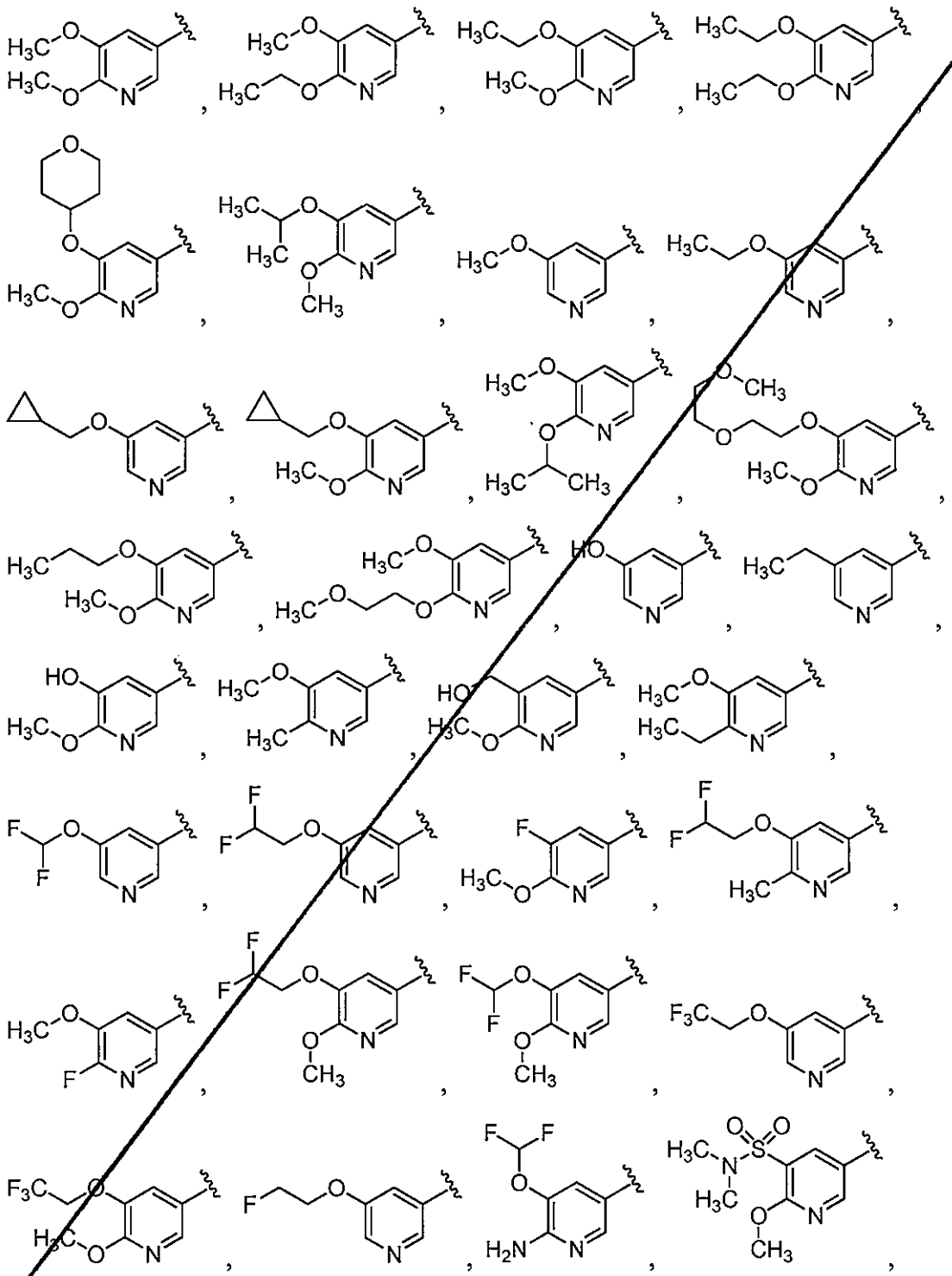
26. The compound according to any one of claims 6 to 14, or a pharmaceutically acceptable salt thereof, wherein each of $R^C$ and $R^D$ is $-OCH_3$.

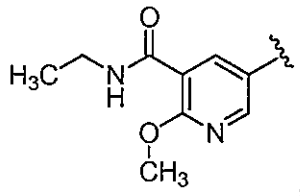
27. The compound according to any one of claims 8 to 14, or a pharmaceutical acceptable salt thereof, wherein $R^D$ is -C(O)OH, $-C(O)N(R^{1b})_2$, -CN, $-S(O)_2C_{1-8}$aliphatic, or $-S(O)_2N(R^{1b})_2$.

28. The compound according to any one of claims 8 to 14, or a pharmaceutically acceptable salt thereof, wherein each of $R^C$ and $R^D$ is, independently, hydrogen, fluoro, chloro, $C_{1-3}$aliphatic, $CF_3$, $-OCF_3$, $-OCHF_2$, or $-OC_{1-2}$aliphatic, wherein at least one of $R^C$ and $R^D$ is not hydrogen.

29. The compound according to claim 28, or a pharmaceutical acceptable salt thereof, wherein $R^C$ is hydrogen and $R^D$ is $-OC_{1-3}$alkyl, optionally substituted with up to 3 F atoms.

30. The compound according to any one of claims 8 to 14, or a pharmaceutical acceptable salt thereof, wherein  is selected from:

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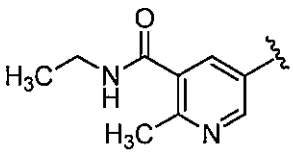
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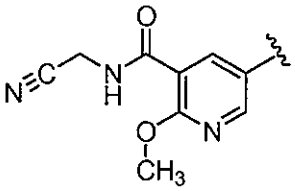
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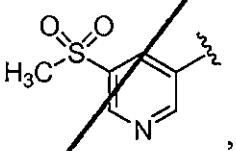
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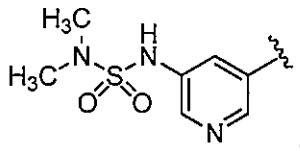
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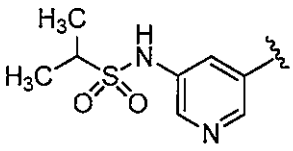
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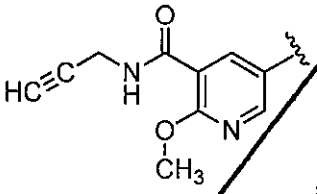
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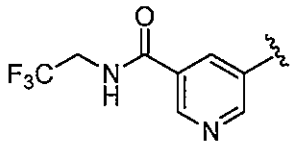
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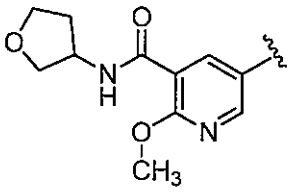
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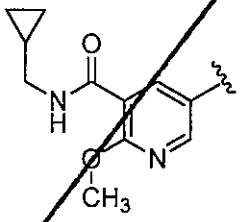
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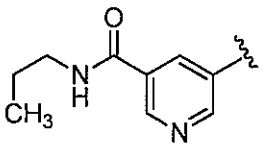
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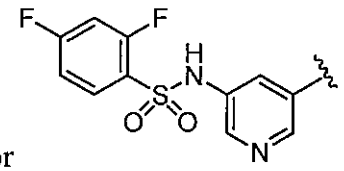

or .

31. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is a compound selected from Table 1.

32. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

33. The composition according to claim 32, additionally comprising a therapeutic agent selected from an agent for treating multiple sclerosis, an anti-inflammatory agent, an immunomodulatory agent, or an immunosuppressive agent.

34. The composition according to claim 33, wherein said therapeutic agent is beta interferon, glatiramir, natalizumab, or mitoxantrone.

35. A method of treating or lessening the severity of a disease or condition selected from an autoimmune disease or an inflammatory disease of the brain or spinal cord selected from multiple sclerosis, epilepsy, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, or amyotrophic lateral sclerosis, comprising the step of administering to said patient a compound or salt thereof according to any one of claims 1 to 14 or 31, or a pharmaceutical composition thereof.

36. The method according to claim 35, wherein said disease or disorder is multiple sclerosis.

37. The method according to claim 35, comprising the additional step of administering to said patient an additional therapeutic agent, wherein said additional therapeutic agent is appropriate for the disease being treated and said additional therapeutic agent is administered together with said compound or composition as a single dosage form or separately from said compound or composition as part of a multiple dosage form.

38. The method according to claim 37, wherein said additional therapeutic agent is useful for treating multiple sclerosis and is selected from beta interferon, glatiramir, natalizumab, or mitoxantrone.

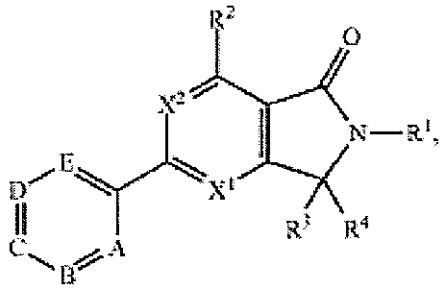
39. A method of inhibiting PI3K-gamma kinase activity in a biological sample comprising contacting said biological sample with a compound according to any one of claims 1 to 14 or 31, or a composition comprising said compound.

## CLAIMS

What is claimed is:

1. A compound having the formula:

(I)



or a pharmaceutically acceptable salt thereof, wherein:

$X^1$ is N;

$X^2$ is CH;

$R^1$ is a pyrazol-4-yl optionally substituted with 1 or 2 independent occurrences of $R^{1a}$;

$R^{1a}$ is chloro, fluoro, $C_{1-8}$aliphatic, $—(CH_2)_{0-2}C_{3-6}$cycloaliphatic, $—(CH_2)_{0-2}$-5-6 membered heterocyclic ring, —CN, $—C(O)C_{1-4}$aliphatic, $—C(O)NH(C_{1-4}$aliphatic), $—C(O)N(C_{1-4}$aliphatic$)_2$, $—C(O)OC_{1-4}$aliphatic, $—S(O)_2NH(C_{1-4}$aliphatic), $—S(O)_2N(C_{1-4}$aliphatic$)_2$, or $—S(O)_2C_{1-4}$aliphatic, wherein up to 3 non-adjacent carbon atoms of said aliphatic or cycloaliphatic of $R^{1a}$ can be substituted for by —O—, —S—, or $—N(R^{1b})—$, wherein said heterocyclic ring has up to two heteroatoms selected from nitrogen, oxygen, or sulfur, and wherein each of said aliphatic, cycloaliphatic, or heterocyclic of $R^{1a}$ is optionally and independently substituted with up to 4 occurrences of $J^R$;

each $J^R$ is independently fluoro, oxo, $—(CH_2)_{0-2}CN$, $—(CH_2)_{0-2}CF_3$, $—C(O)R^{1b}$, $—C(O)N(R^{1b})_2$, $—C(O)O(R^{1b})$, $—N(R^{1b})_2$, $—N(R^{1b})C(O)R^{1b}$, $—(CH_2)_{0-2}OR^{1b}$, phenyl, 5-6 membered heteroaryl, 4-6 heterocyclyl, 9-11 fused bicyclic heteroaryl, or 9-11 fused bicyclic heterocyclyl, wherein each of said heteroaryl or heterocyclyl rings having up to 3 atoms selected from nitrogen, oxygen, or sulfur, and wherein each of said cycloaliphatic, phenyl, heteroaryl, or heterocyclyl is optionally substituted with up to 2 $R^{1c}$;

each $R^{1b}$ is, independently, selected from hydrogen, $C_{1-8}$aliphatic, $—(CH_2)_{0-1}C_{3-6}$cycloaliphatic,

—$(CH_2)_{0-3}C_{4-6}$heterocyclic having up to two heteroatoms selected from N or O, or two $R^{1b}$ together with the atom to which they are bonded form a 5-6 membered heterocyclic ring, wherein each aliphatic, cycloaliphatic, or heterocyclic is optionally substituted with up to three F atoms or up to two —OH, —$C_{1-2}$alkyl, or —$OC_{1-2}$alkyl groups;

each $R^{1c}$ is, independently, fluoro, chloro, $C_{1-4}$aliphatic, —$(CH_2)_{0-2}$OH, —CN, —$C(O)C_{1-4}$aliphatic, or —$C(O)OC_{1-4}$aliphatic;

$R^2$ is hydrogen or $C_{1-2}$aliphatic;

$R^3$ is hydrogen, $C_{1-6}$aliphatic, $C_{3-6}$ cycloaliphatic, $C_{4-7}$ heterocyclyl having 1 or 2 atoms selected from N or O, —$(CH_2)_{0-3}CF_3$, —OH, —$OC_{1-6}$aliphatic, —$OC_{3-6}$cycloaliphatic, —$OC_{3-6}$heterocyclyl having one oxygen atom, —$O(CH_2)_2OC_{1-2}$aliphatic, —$OC_{1-2}$alkylC(O)$OC_{1-3}$aliphatic, or benzyl; and

$R^4$ is hydrogen or $C_{1-6}$alkyl, wherein at least one of $R^3$ or $R^4$ is not hydrogen; or $R^3$ and $R^4$ together with the carbon to which they are bonded form a 3-6 membered cycloaliphatic ring, a 3-6 membered heterocyclic ring having up to two atoms selected from N or O, or a $C_2$alkenyl, wherein each of said aliphatic, cycloaliphatic, or heterocyclyl of $R^3$, $R^4$, or $R^3$ and $R^4$ together is optionally substituted with up to three F atoms, or up to two $C_{1-2}$alkyl, —$C(O)C_{1-4}$alkyl, —$C(O)OC_{1-4}$alkyl, —OH, or —$OC_{1-2}$alkyl groups;

A is $CR^A$ wherein $R^A$ is hydrogen;

B is N;

C is $CR^C$;

D is $CR^D$;

E is $CR^E$ wherein $R^E$ is hydrogen;

$R^C$ is hydrogen, F, Cl, $C_{1-3}$aliphatic, —$(CH_2)_{0-1}CF_3$, —$(CH_2)_{0-1}CHF_2$, —$N(R^{1b})_2$, —OH, —$O(CH_2)_{0-1}CF_3$, or —$OC_{1-8}$aliphatic, wherein up to 2 non-adjacent carbon atoms of said aliphatic can be substituted for by —O—;

$R^D$ is hydrogen, fluoro, chloro, $C_{1-4}$aliphatic, —C(O)OH, —$C(O)OC_{1-4}$aliphatic, —$C(O)N(R^{1b})_2$, —CN, —$C(R^{D1})$=N—$OR^{1b}$, —$N(R^{1b})_2$, —$N(R^{D1})C(O)C_{1-4}$aliphatic, —$N(R^{D1})C(O)$phenyl, —$N(R^{D1})S(O)_2C_{1-4}$aliphatic, —$N(R^{D1})S(O)_2N(R^{1b})_2$, —$N(R^{D1})S(O)_2$phenyl, —OH, —$OC_{1-8}$aliphatic, —$O(CH_2)_{0-1}C_{3-6}$ cycloaliphatic, —$SC_{1-4}$aliphatic, —$S(O)C_{1-4}$aliphatic, —$S(O)_2C_{1-4}$aliphatic, or —$S(O)_2N(R^{1b})_2$; wherein up to 2 non-adjacent carbon atoms of said aliphatic, cycloaliphatic, or heterocyclic of $R^D$ can be substituted for by —O— and each of said aliphatic, cycloaliphatic, or phenyl of $R^D$ can be substituted with up to 5 fluorine atoms; or $R^D$ and $R^C$ together with the atoms to which they are attached form a phenyl or pyridyl ring; and

each $R^{D1}$ is, independently, hydrogen or $C_{1-2}$alkyl.

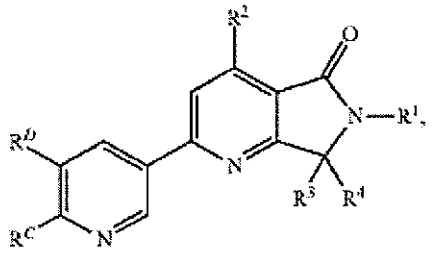
2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is 1-(2,2-difluoroethyl)-1H-pyrazol-4-yl or 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl.

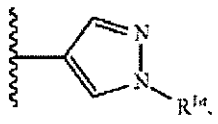
3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of $R^C$ and $R^D$ is —$OCH_3$.

4. A compound having the formula:

(I-A)



or a pharmaceutically acceptable salt thereof, wherein $R^1$ is



wherein

$R^{1a}$ is —$C_{1-4}$alkyl optionally and independently substituted with —CN, up to three F atoms, up to two $CH_3$, up to two —$OC_{1-2}$alkyl, or up to two —OH groups;

$R^2$ is $C_{1-2}$alkyl;

$R^3$ is hydrogen, —OH, —$OC_{1-4}$ alkyl, or $C_{1-4}$alkyl optionally substituted with up to two —OH groups;

$R^4$ is hydrogen or $CH_3$, wherein at least one of $R^3$ and $R^4$ is not hydrogen; or $R^3$ and $R^4$ together form a $C_{3-6}$cycloalkyl ring optionally substituted with up to two OH groups; or $R^3$ and $R^4$ together form a 4-6 membered heterocyclic ring having one oxygen or a nitrogen atom optionally substituted with $C_{1-4}$alkyl, —$C(O)C_{1-4}$alkyl, or $C(O)OC_{1-4}$alkyl;

$R^C$ is hydrogen, F, $C_{1-2}$alkyl, or —$OC_{1-2}$alkyl; and

$R^D$ is —$OR^{D1}$, —$C(O)N(R^{D1})R^{D2}$, —$S(O)_2N(R^{D1})R^{D2}$, —$S(O)_{1-2}R^{D2}$, —$N(R^{D1})S(O)_2R^{D2}$, or —$N(R^{D1})S(O)_2N(R^{D1})R^{D2}$, wherein

$R^{D1}$ is hydrogen or $C_{1-2}$alkyl, and $R^{D2}$ is $C_{1-4}$alkyl, —$(CH_2)_{0-1}C_{3-6}$cycloalkyl, or —$(CH_2)_{0-1}C_{4-6}$heterocyclyl, wherein said heterocyclyl has up to two oxygen or nitrogen atoms, and wherein each alkyl of $R^{D1}$ and each alkyl, cycloalkyl, or heterocyclyl of $R^{D2}$ is optionally substituted with up to three F atoms or up to two —OH groups.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein $R^{1a}$ is $C_{1-2}$alkyl, optionally substituted with up to 3 fluorine atoms.

6. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein $R^{1a}$ is $C_{1-2}$alkyl, optionally substituted with CN.

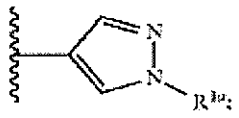
7. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is $CH_3$.

8. The compound according to claim 4, or a pharmaceutical acceptable salt thereof, wherein each of $R^3$ and $R^4$ is $CH_3$.

9. The compound according to claim 4, or a pharmaceutical acceptable salt thereof, wherein $R^3$ and $R^4$ together form a 4-6 membered heterocyclic ring having one oxygen or a nitrogen atom optionally substituted with $C_{1-4}$alkyl, —$C(O)C_{1-4}$alkyl, or —$C(O)OC_{1-4}$alkyl.

10. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ is



$R^2$ is $CH_3$;
$R^3$ is hydrogen, $C_{1-2}$alkyl, OH, or $OCH_3$;
$R^4$ is hydrogen or $CH_3$;
$R^C$ is hydrogen; and
$R^D$ is —$OC_{1-2}$alkyl or —$OC_{3-5}$cycloalkyl, each optionally substituted with up to 3 fluorine atoms.

**11.** The compound according to claim **10**, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is 1-(2,2-difluoroethyl)-1H-pyrazol-4-yl or 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl.

**12.** The compound according to claim **4**, or a pharmaceutically acceptable salt thereof, wherein each of $R^C$ and $R^D$ is —$OCH_3$.

**13.** The compound according to claim **4**, or a pharmaceutical acceptable salt thereof, wherein $R^D$ is —C(O)OH, —$C(O)N(R^{1b})_2$, —CN, —$S(O)_2C_{1-6}$aliphatic, or —$S(O)_2N(R^{1b})_2$.

**14.** The compound according to claim **4**, or a pharmaceutically acceptable salt thereof, wherein each of $R^C$ and $R^D$ is, independently, hydrogen, fluoro, chloro, $C_{1-3}$aliphatic, $CF_3$, —$OCF_3$, —$OCHF_2$, or —$OC_{1-2}$aliphatic, wherein at least one of $R^C$ and $R^D$ is not hydrogen.

**15.** The compound according to claim **14**, or a pharmaceutical acceptable salt thereof, wherein $R^C$ is hydrogen and $R^D$ is —$OC_{1-3}$alkyl, optionally substituted with up to 3 F atoms.

**16.** A compound selected from

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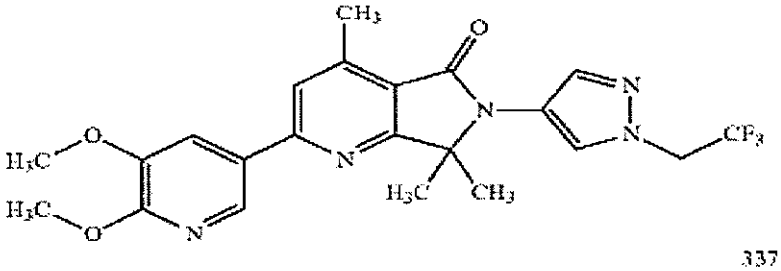

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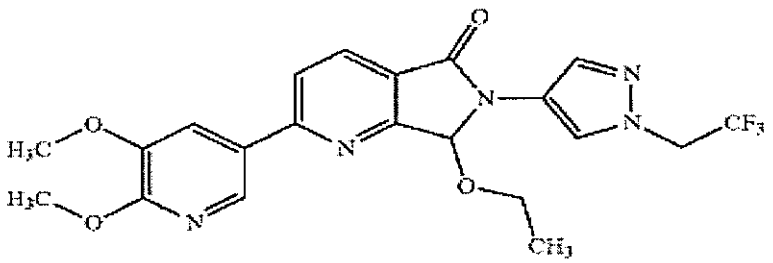

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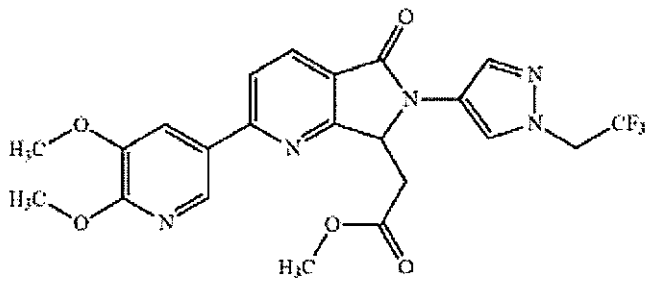

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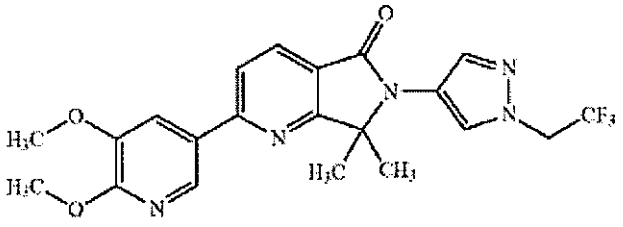

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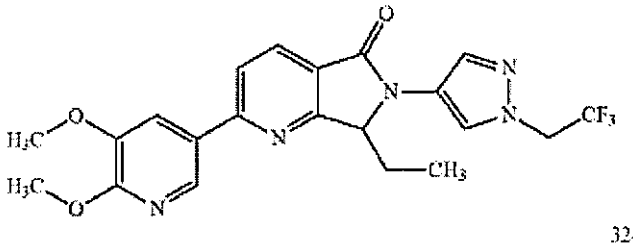

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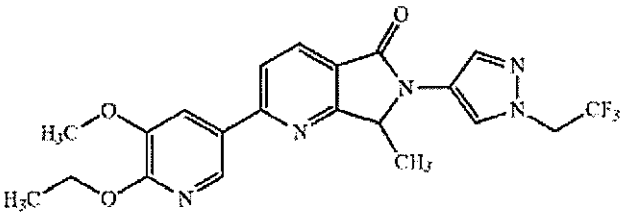

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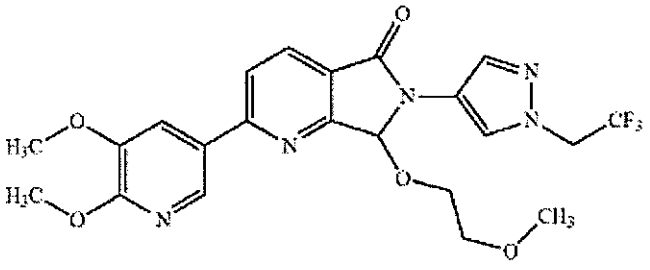

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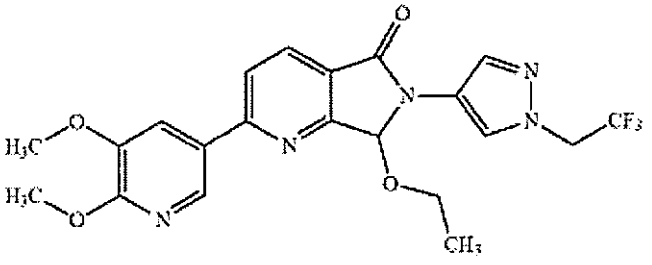

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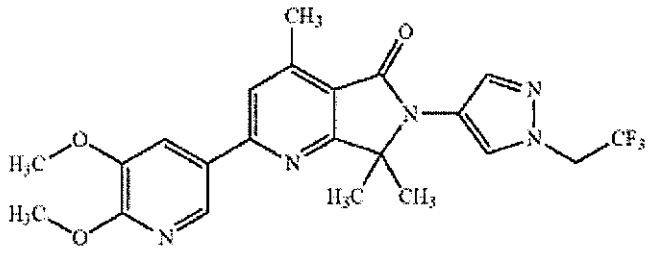

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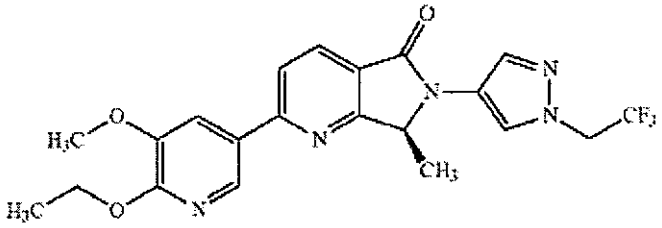

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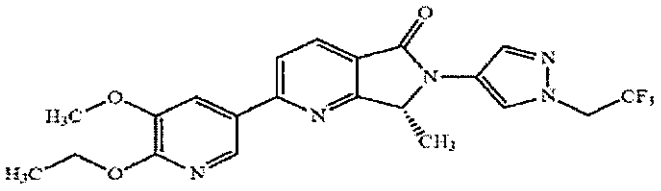

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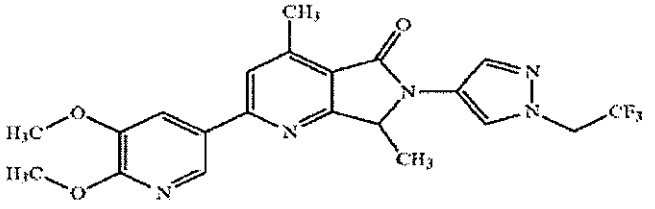

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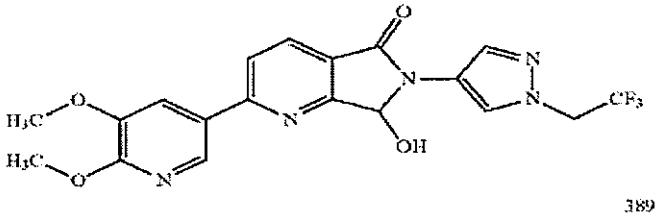

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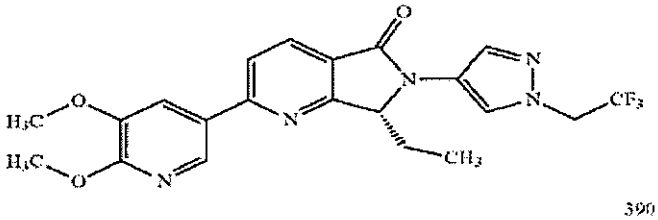

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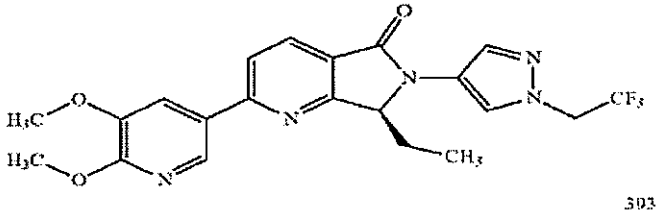

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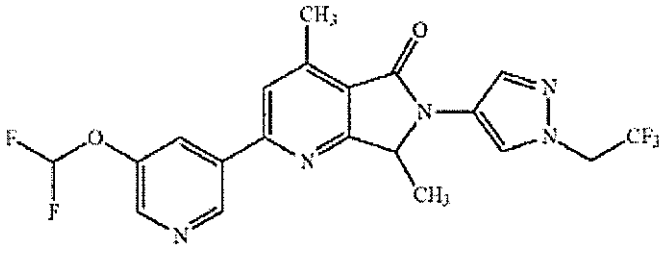

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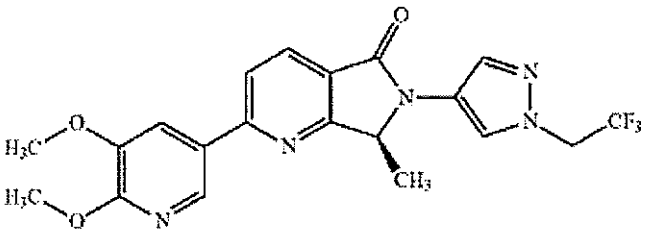

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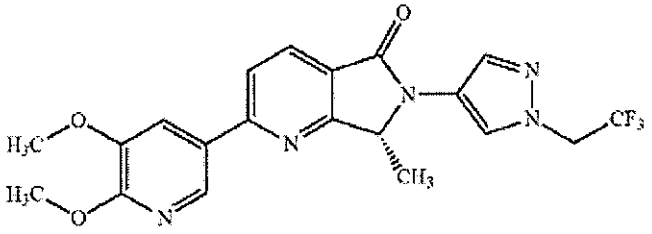

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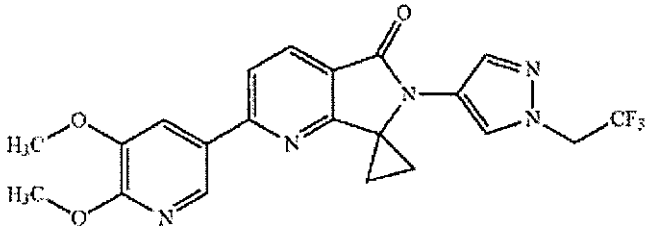

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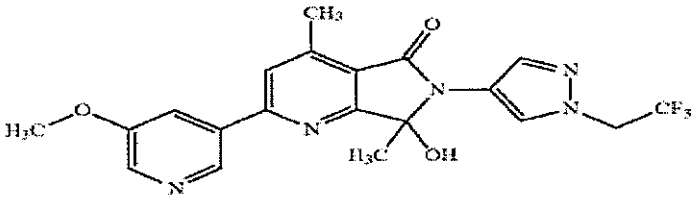

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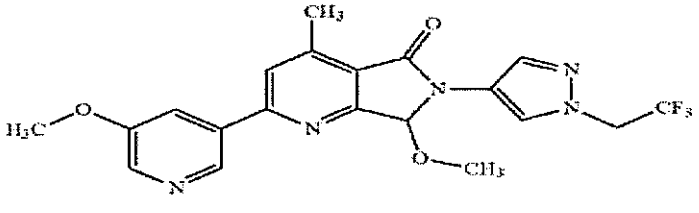

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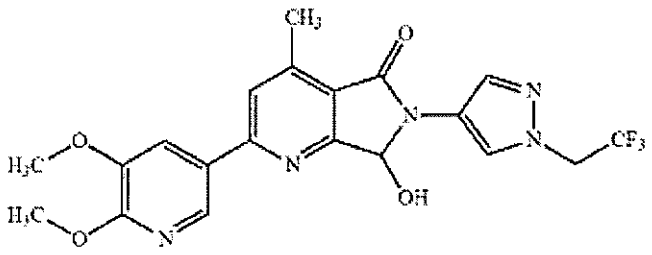

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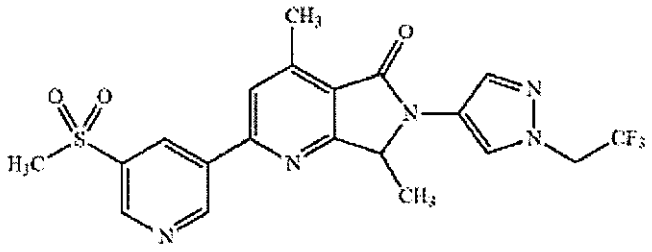

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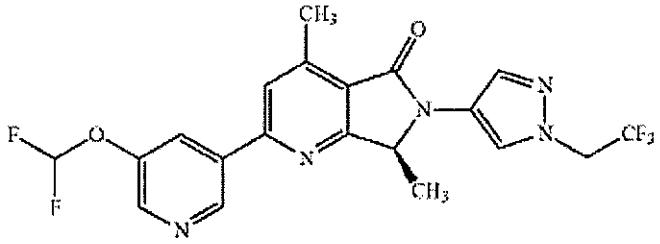

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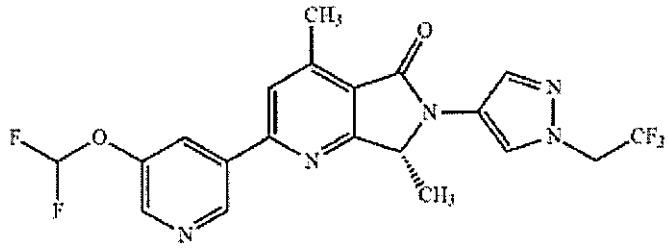

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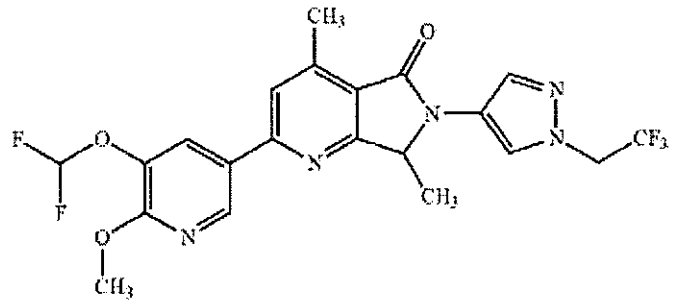

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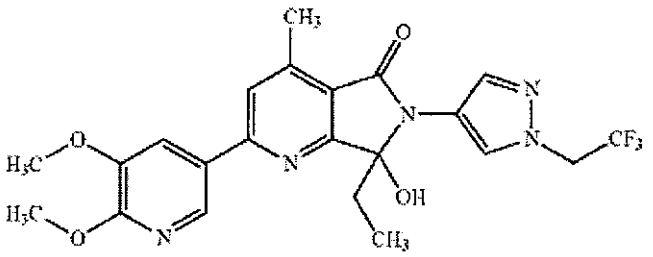

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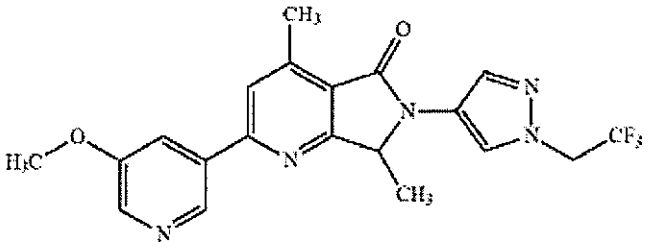

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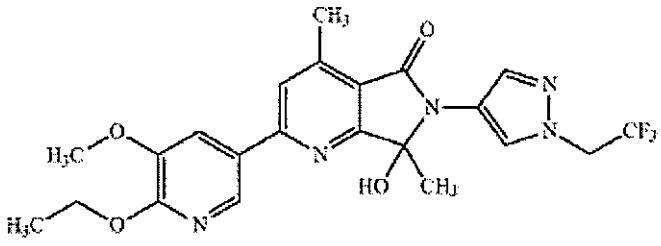

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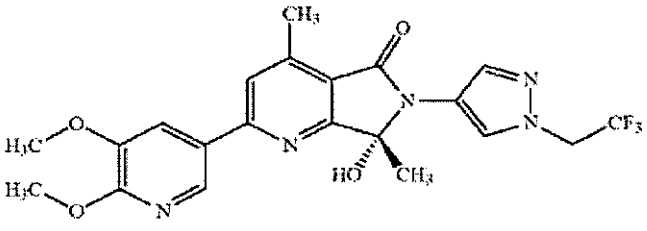

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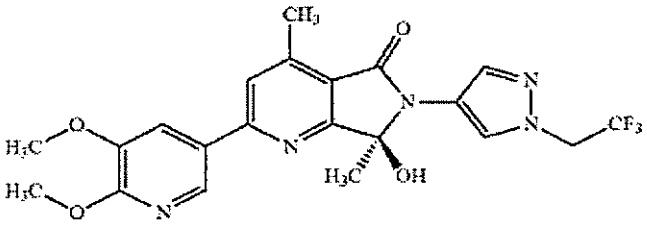

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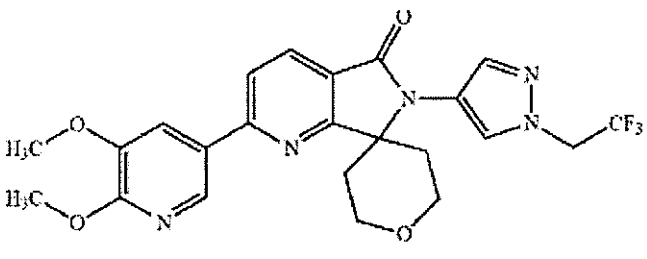

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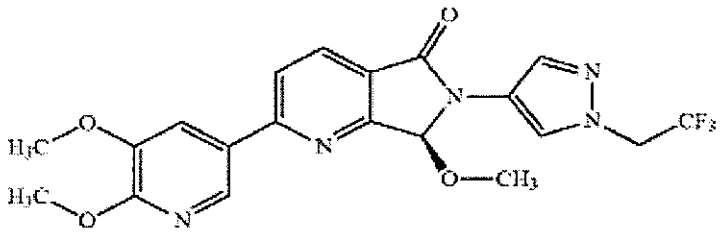

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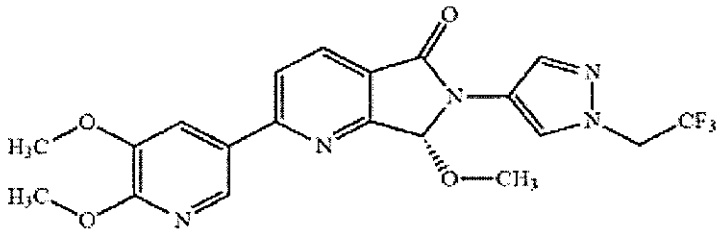

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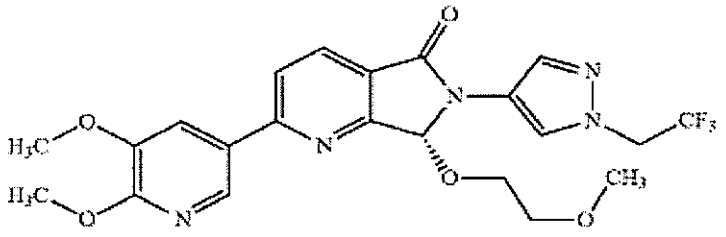

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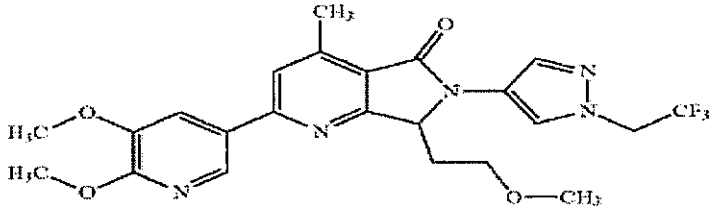

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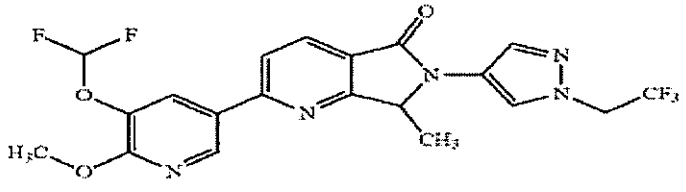

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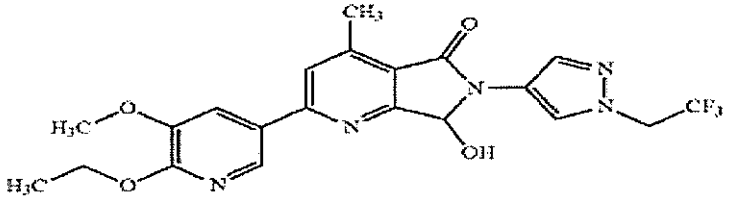

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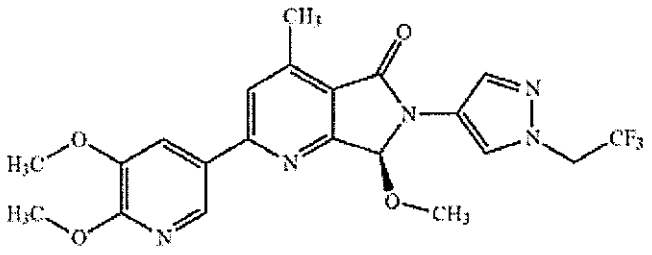

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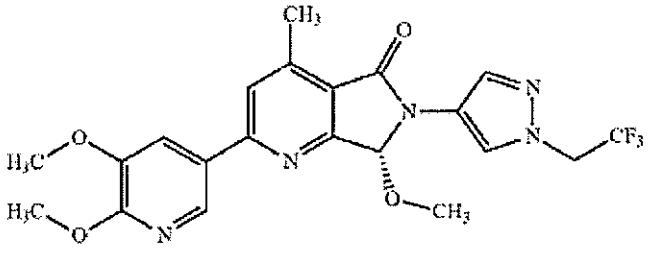

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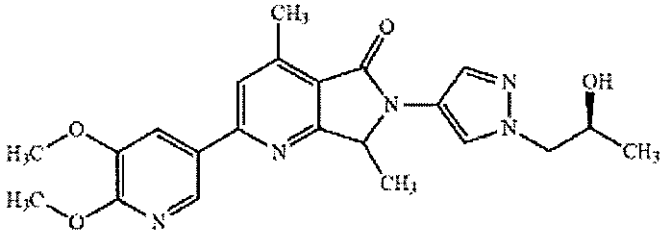

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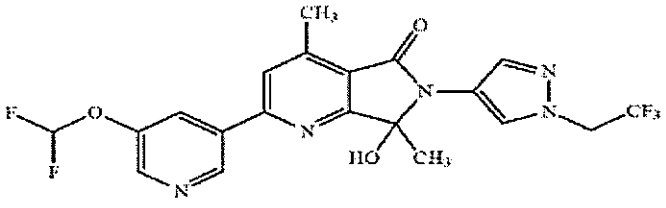

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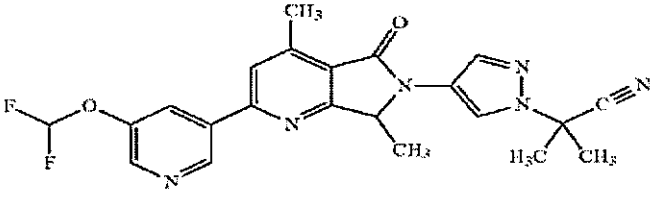

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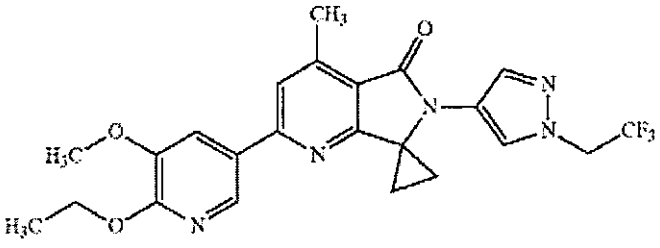

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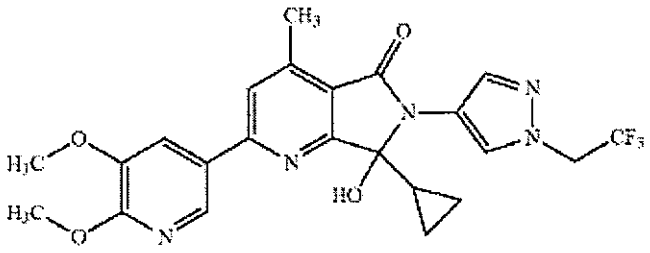

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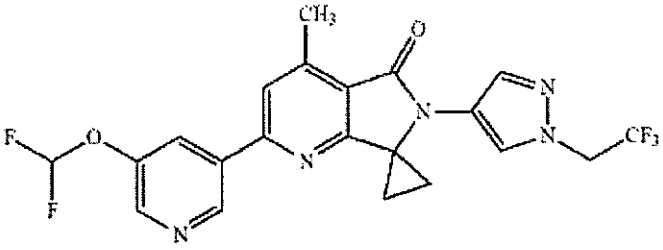

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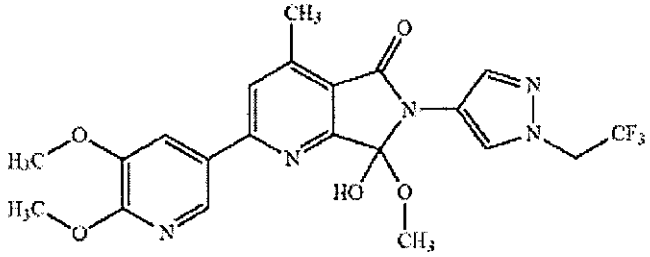

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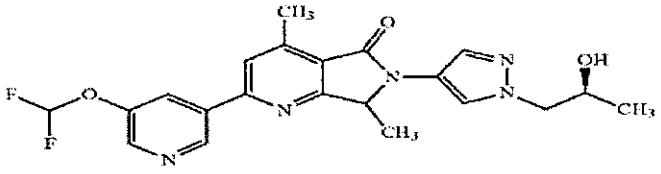

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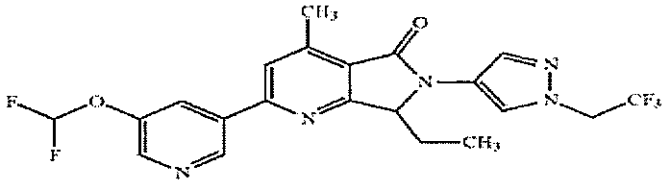

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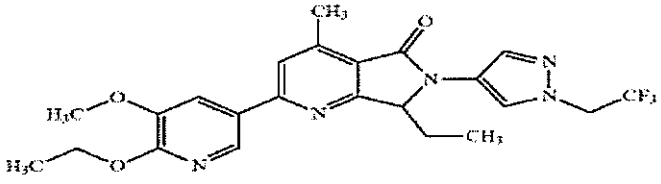

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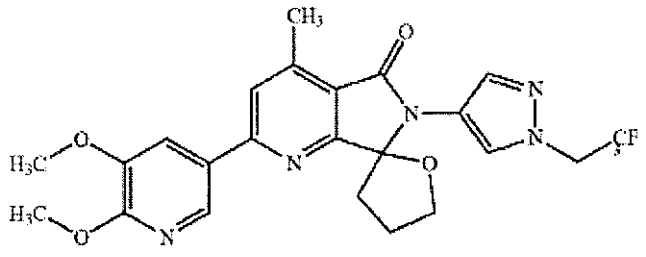

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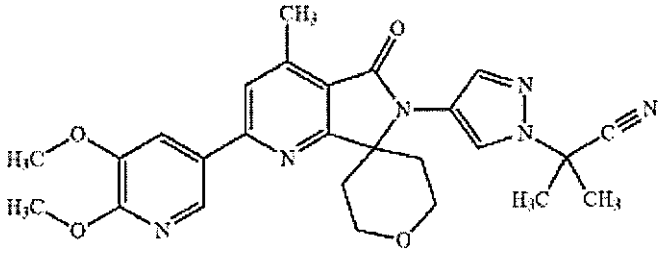

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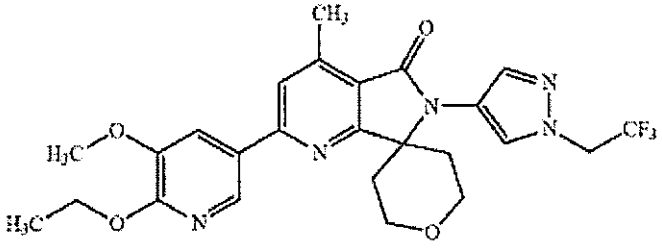

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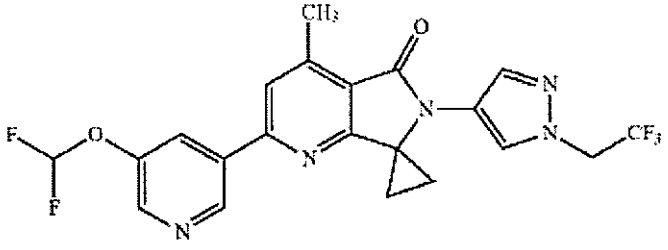

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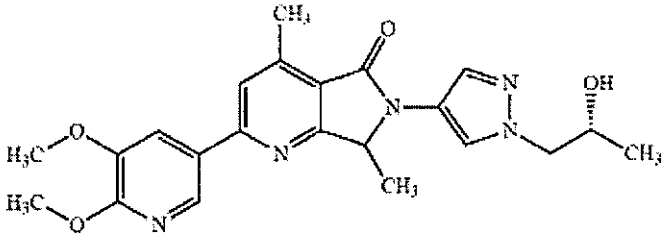

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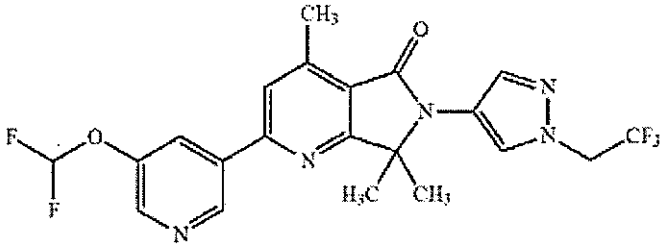

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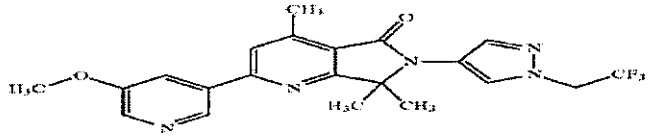

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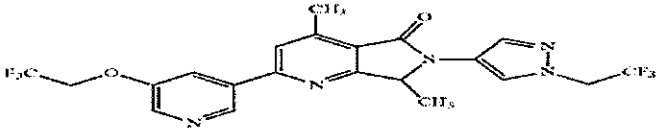

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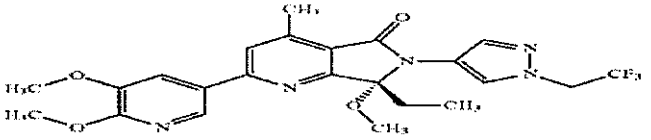

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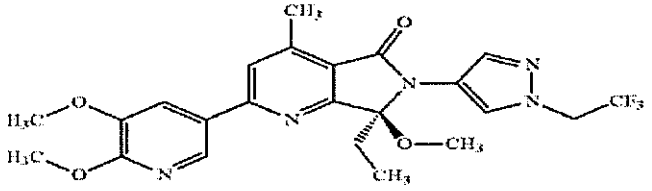

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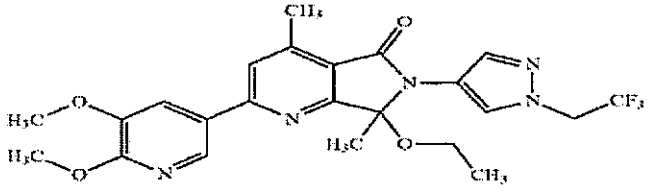

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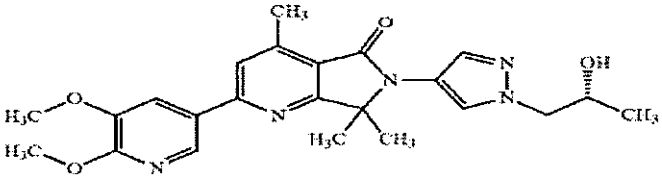

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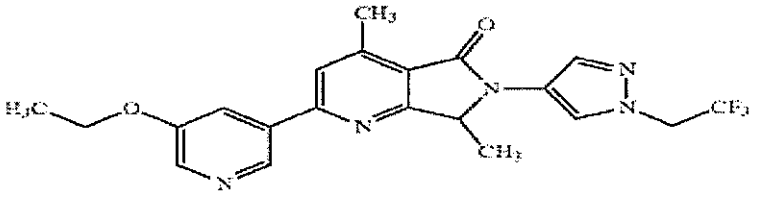

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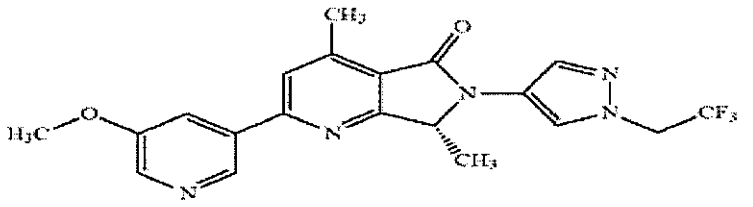

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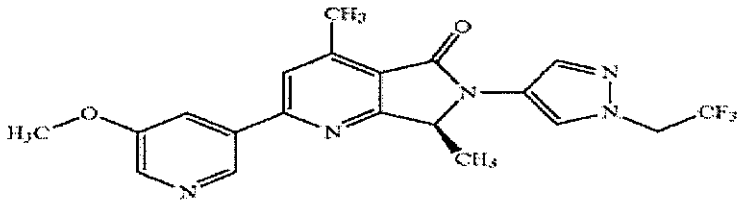

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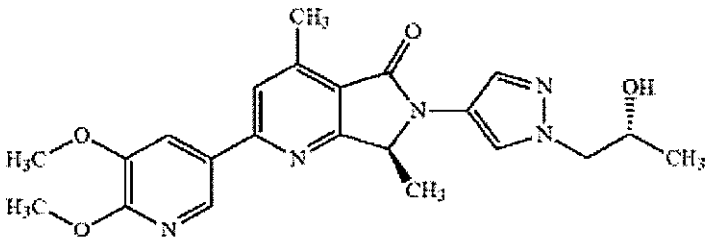

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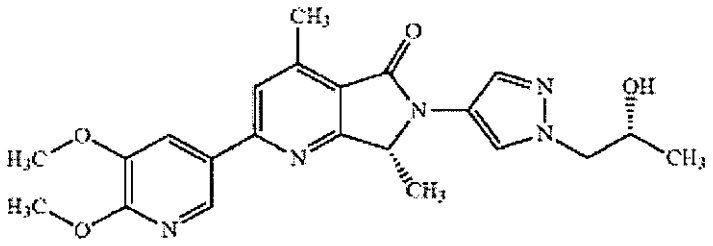

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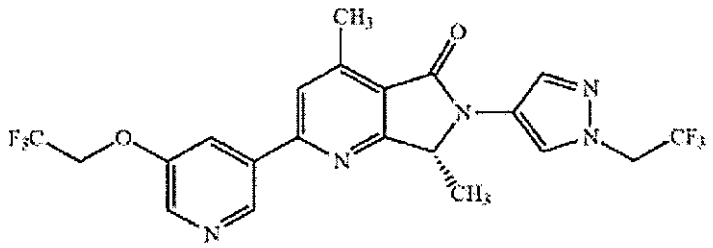

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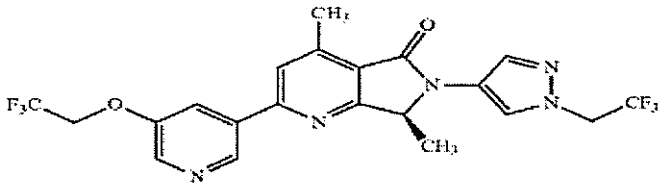

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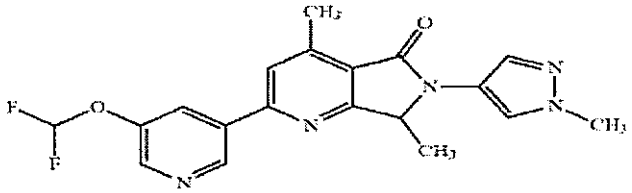

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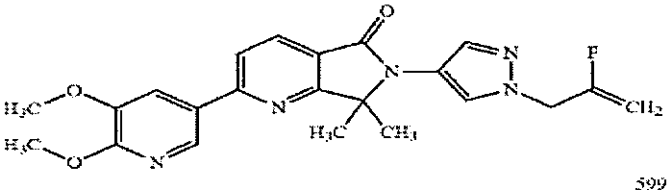

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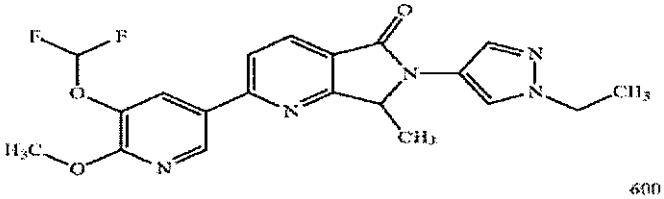

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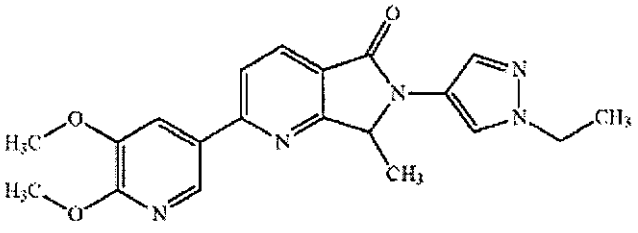

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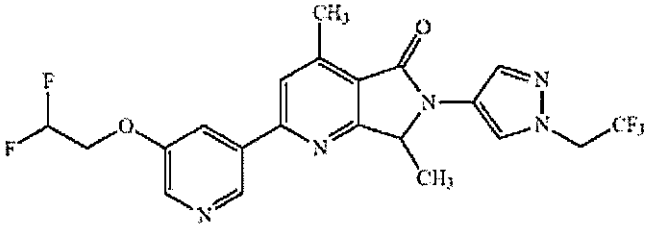

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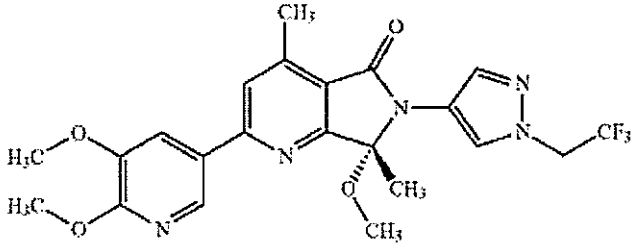

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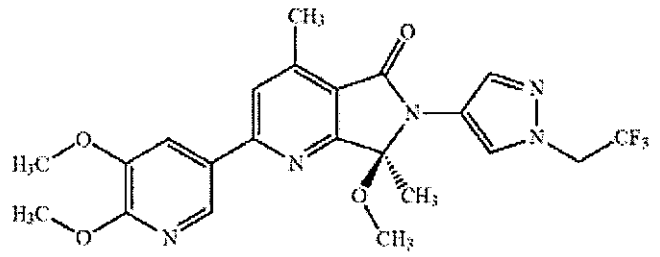

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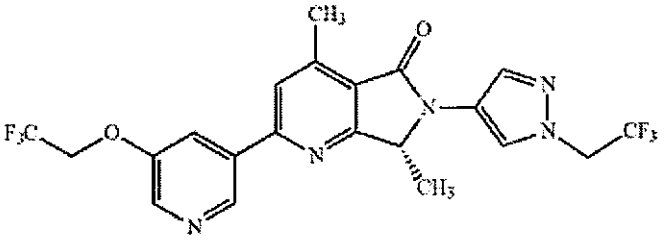

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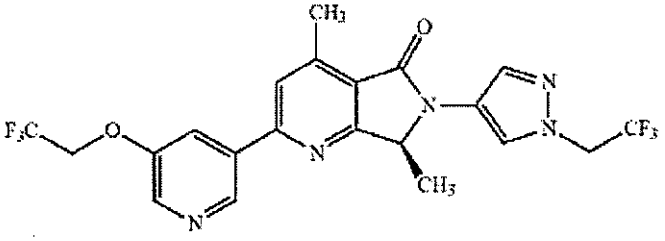

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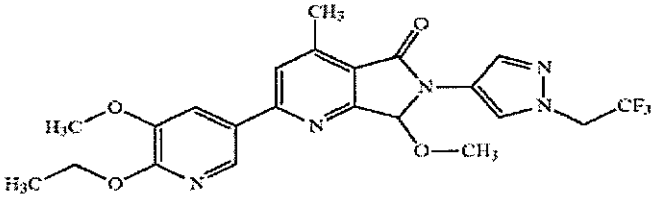

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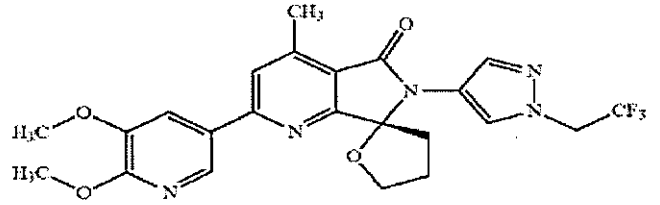

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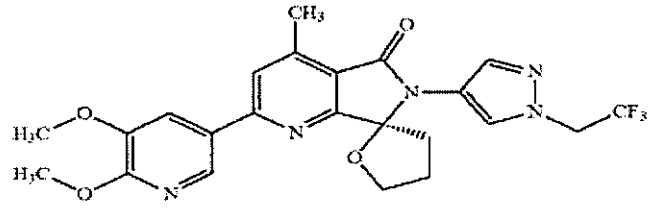

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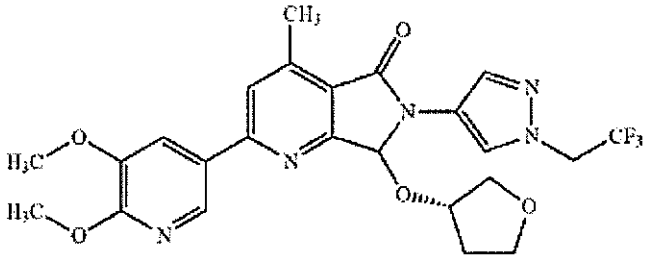

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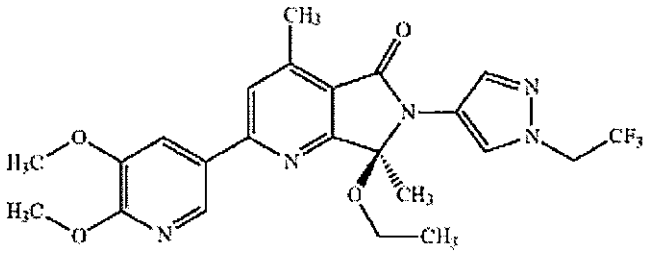

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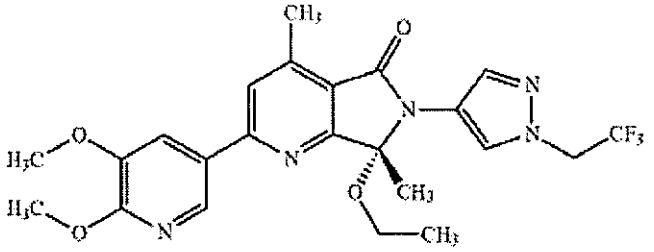

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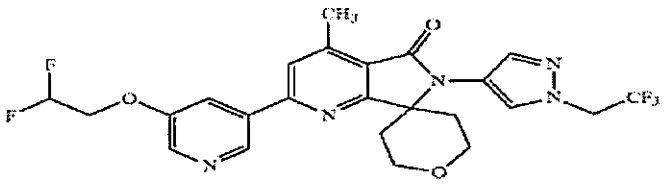

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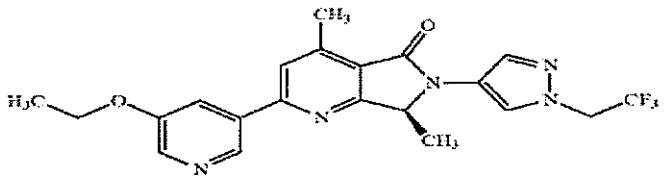

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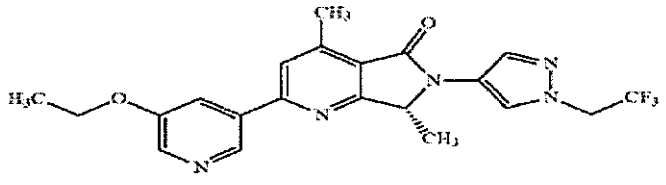

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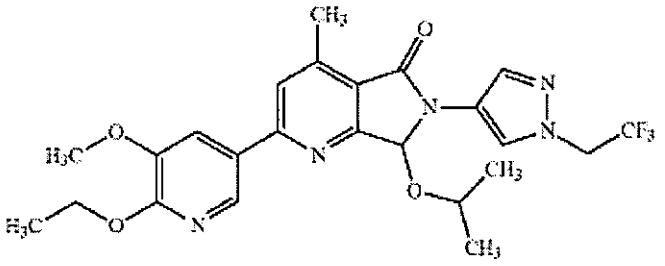

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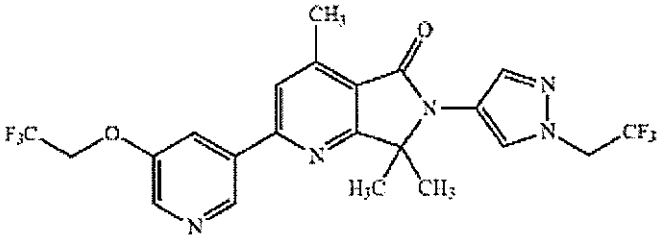

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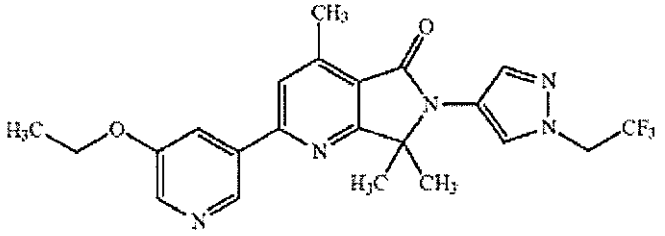

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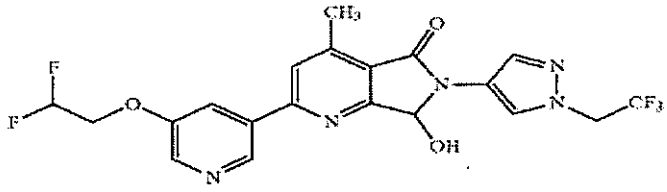

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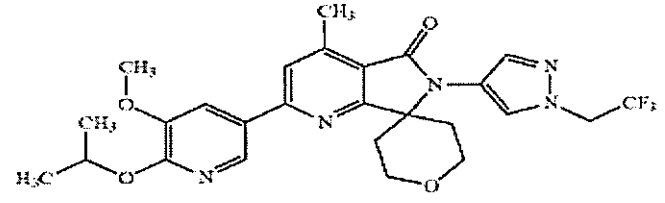

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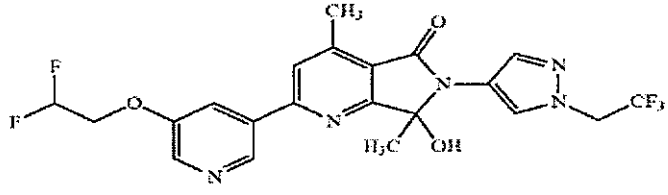

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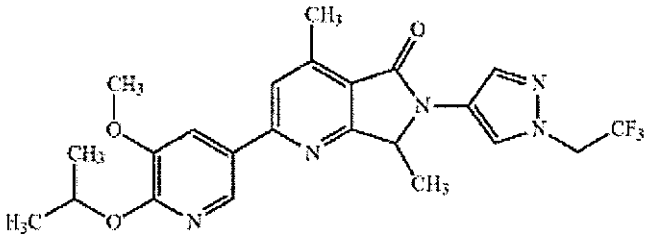

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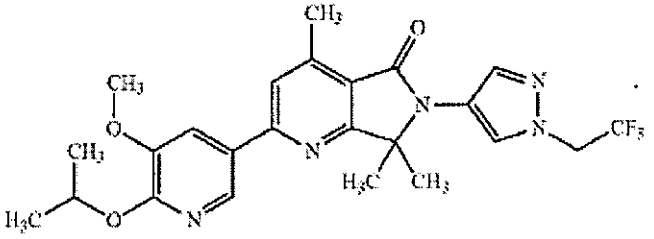

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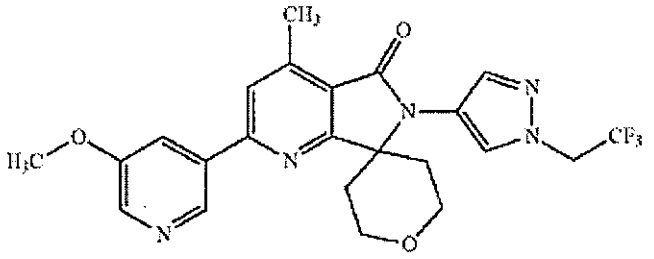

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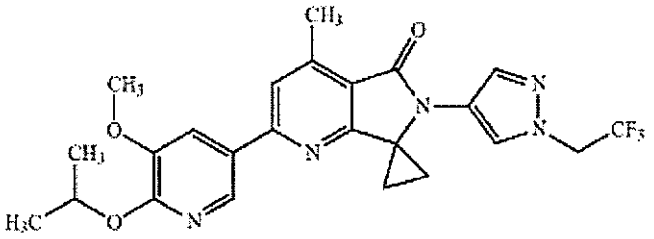

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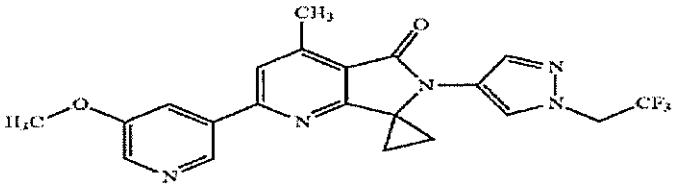

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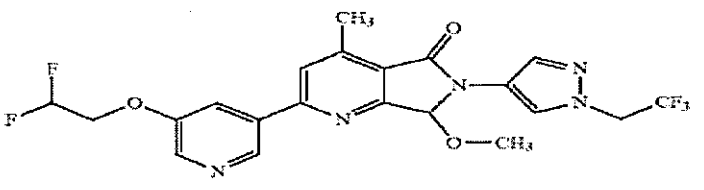

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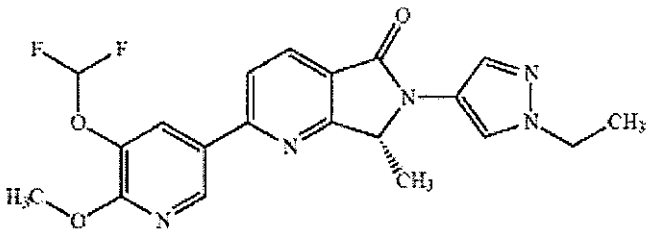

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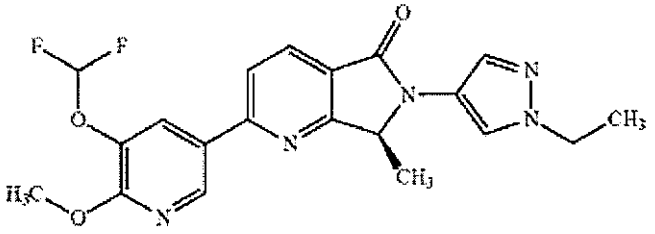

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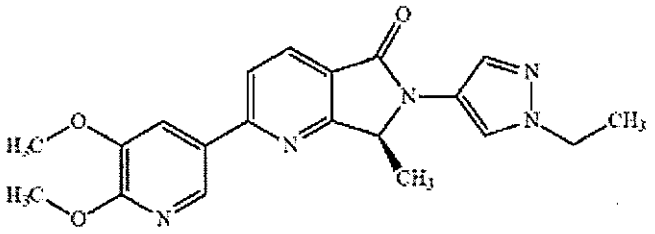

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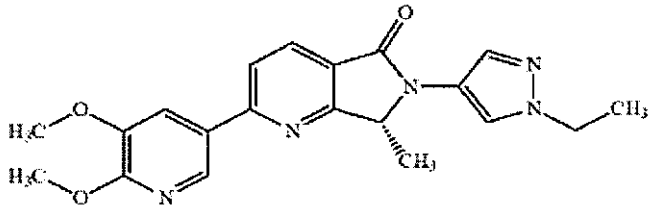

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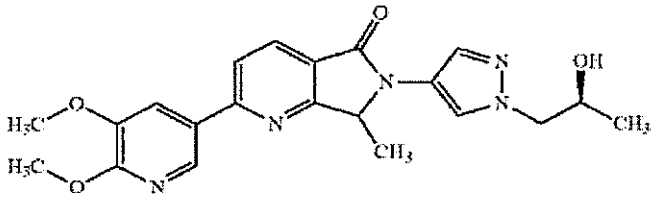

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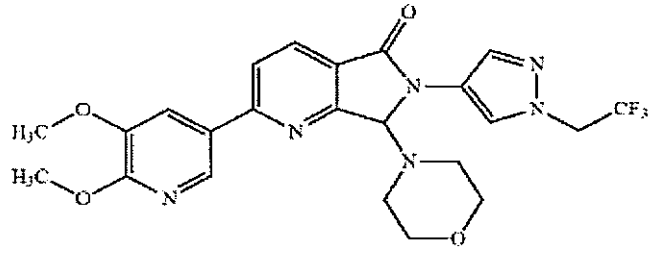

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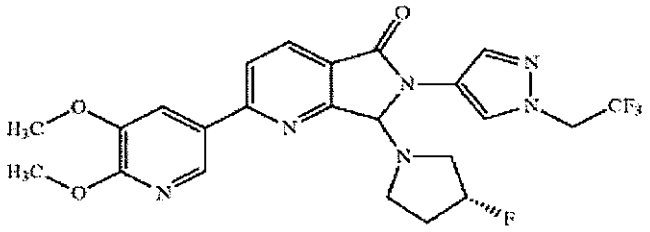

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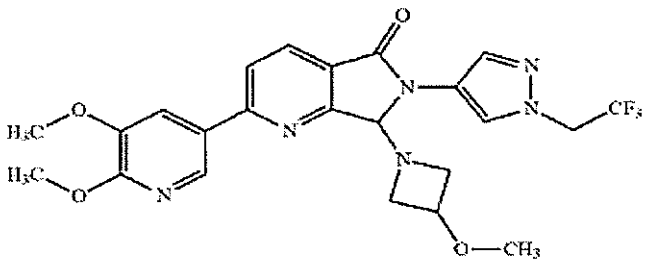

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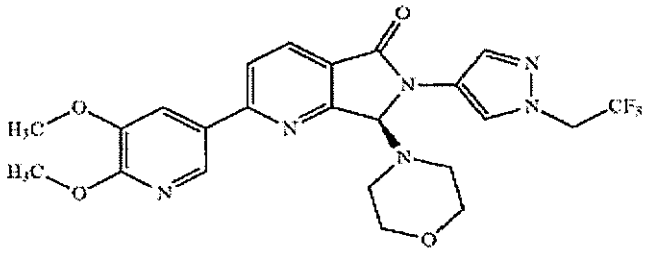

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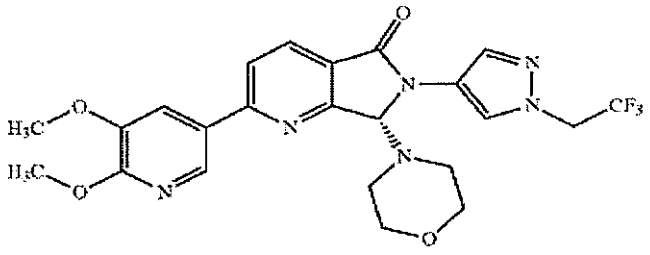

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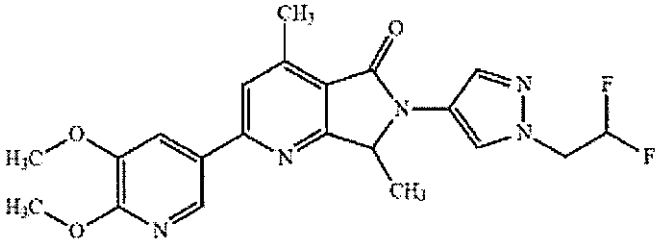

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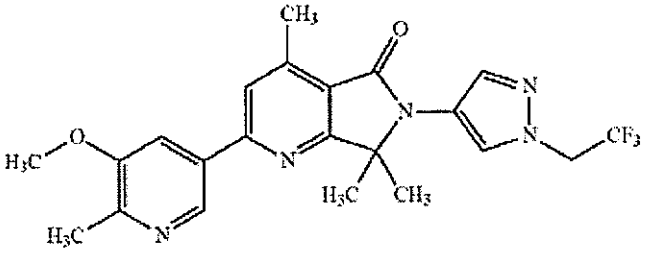

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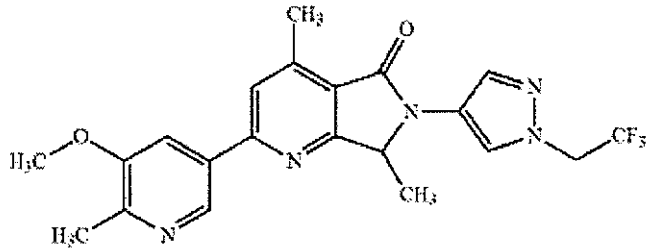

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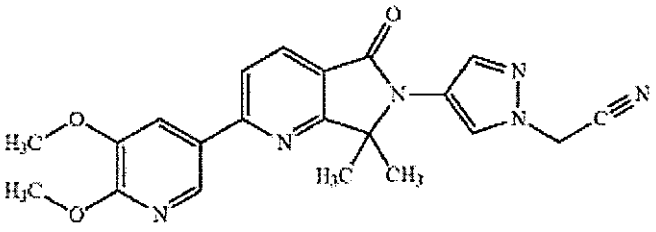

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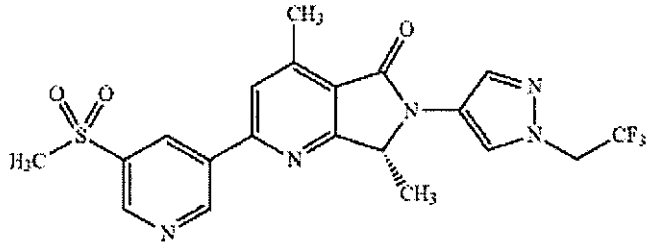

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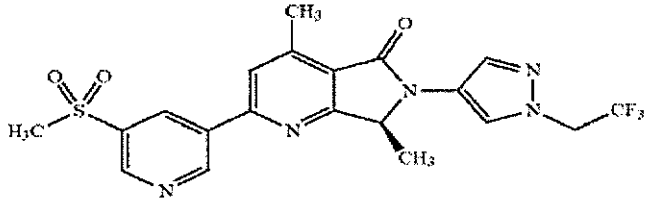

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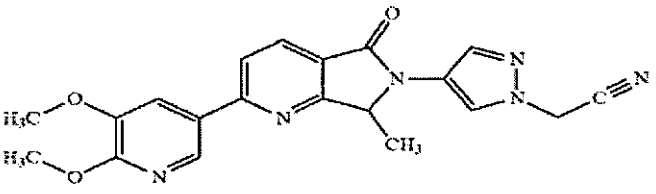

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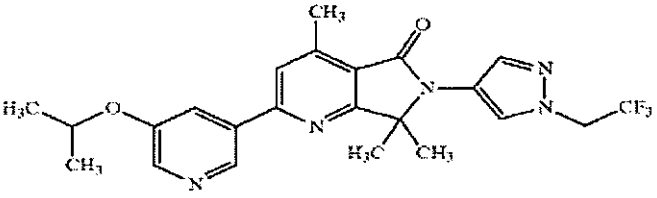

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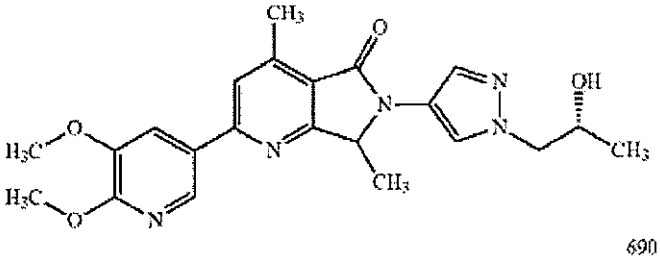

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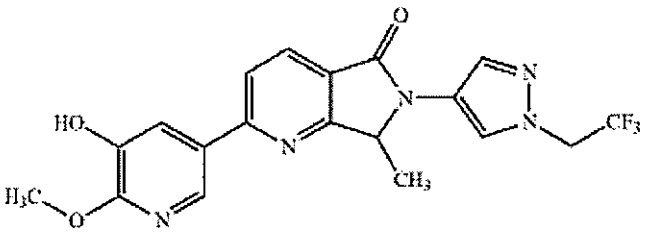

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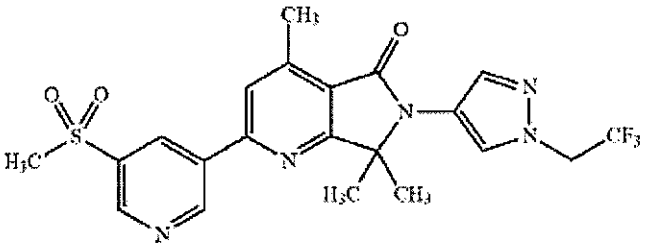

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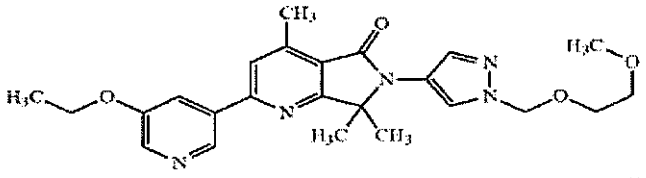

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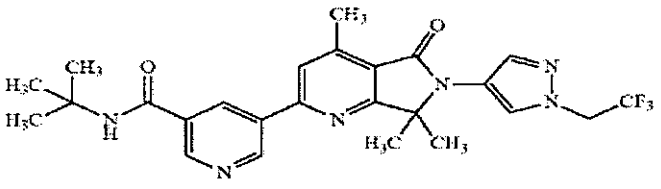

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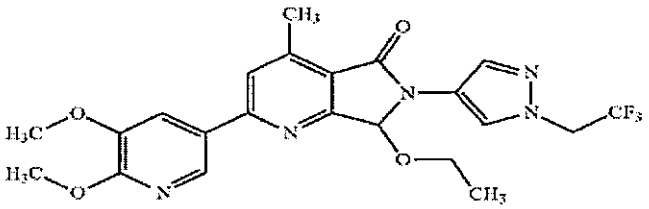

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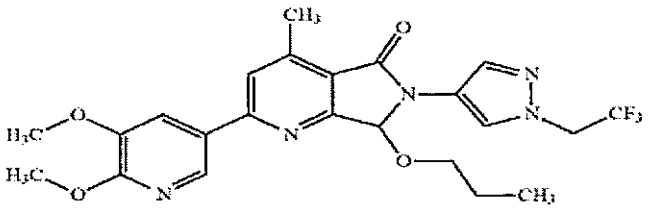

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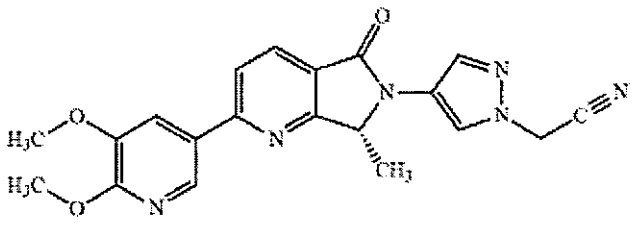

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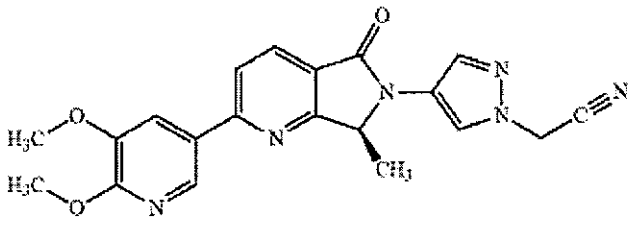

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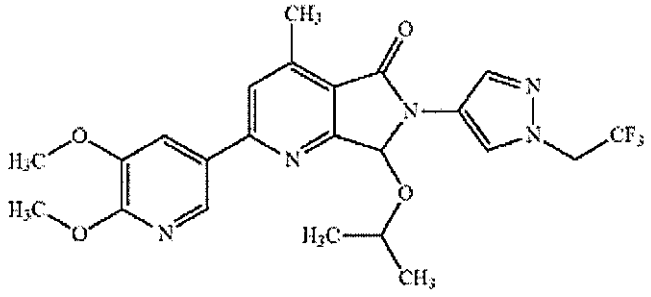

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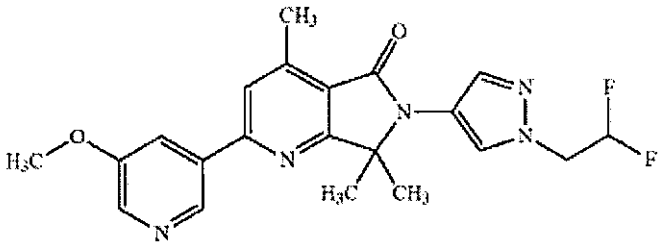

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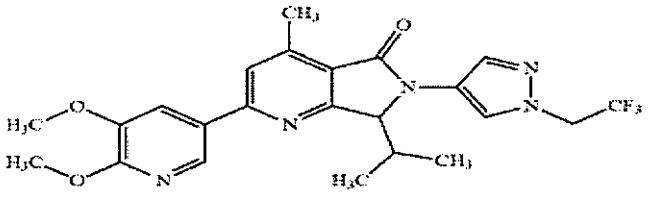

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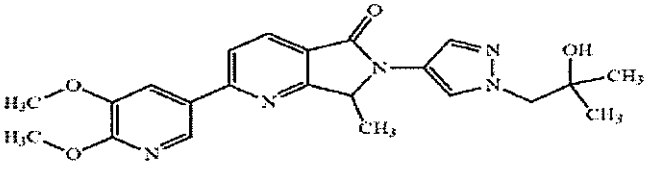

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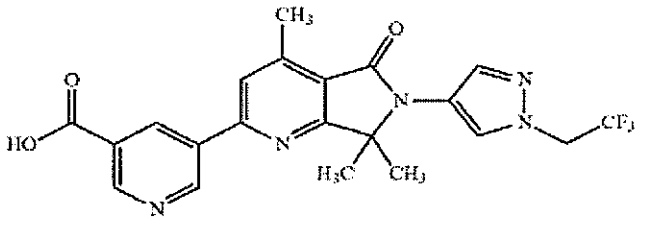

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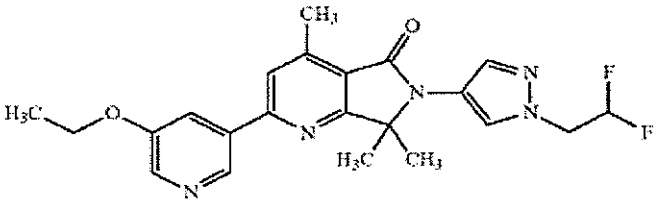

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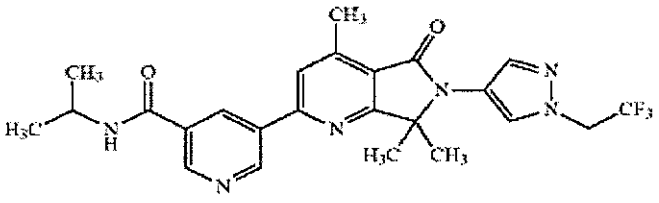

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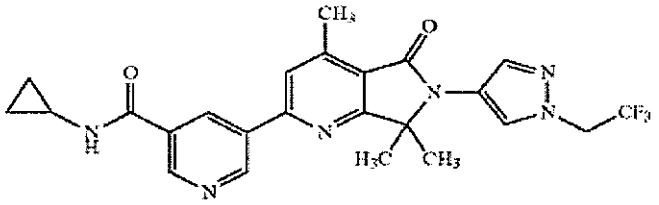

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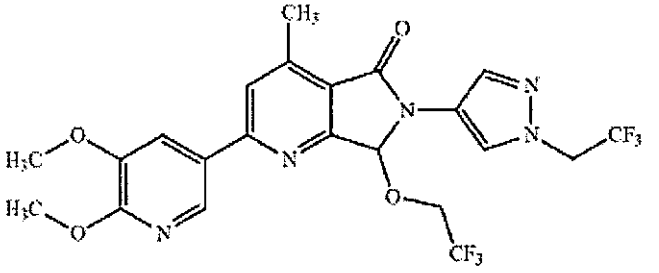

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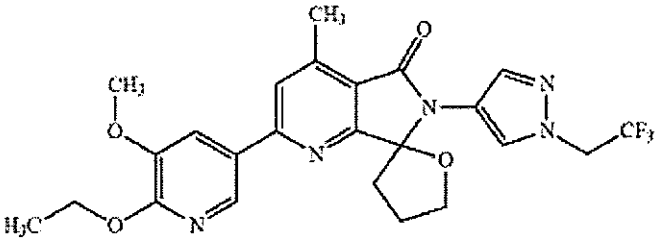

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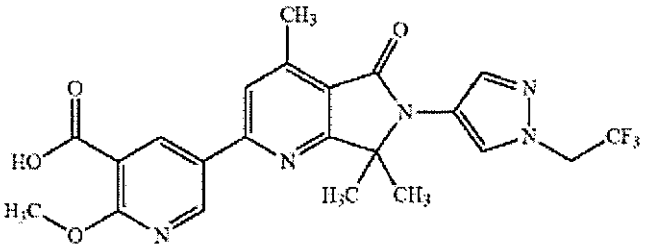

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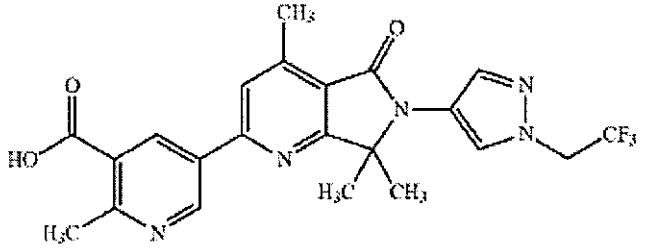

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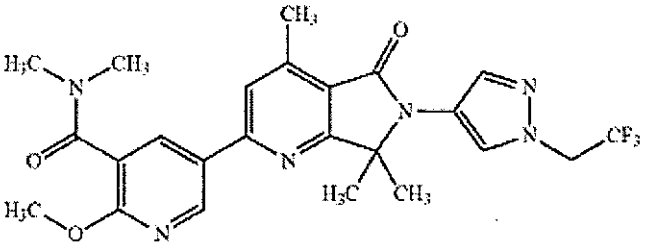

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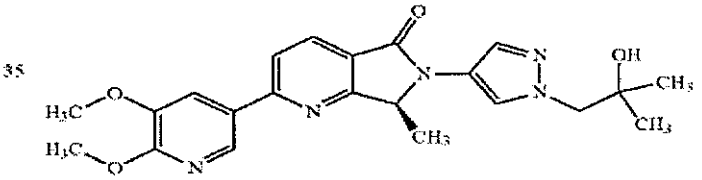

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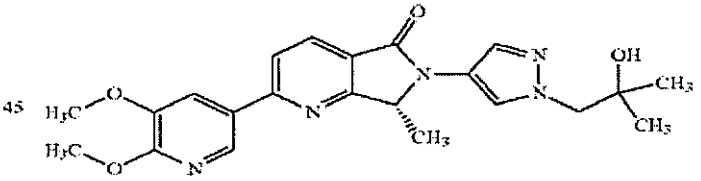

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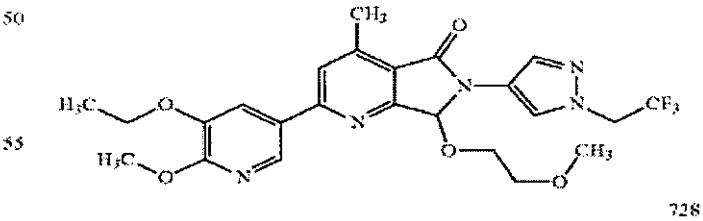

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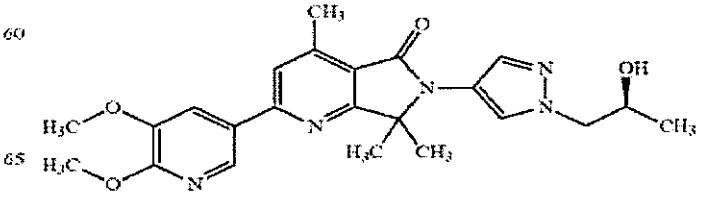

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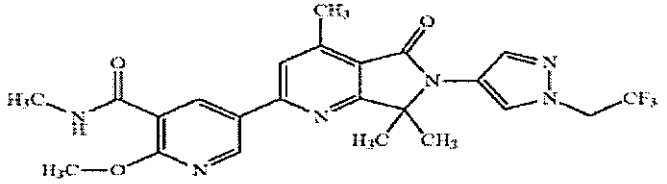

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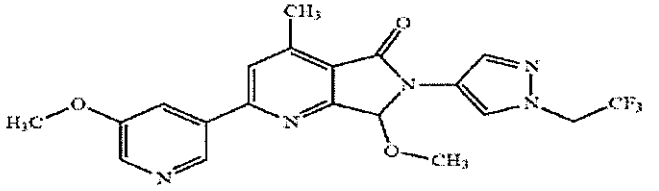

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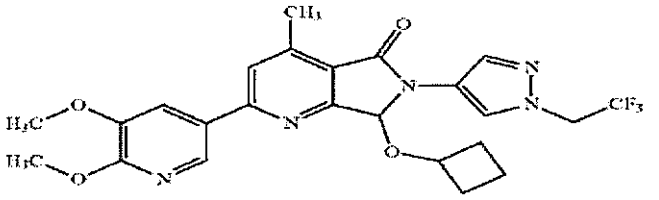

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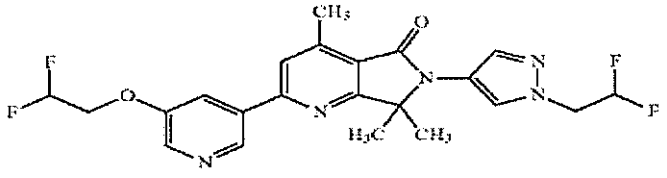

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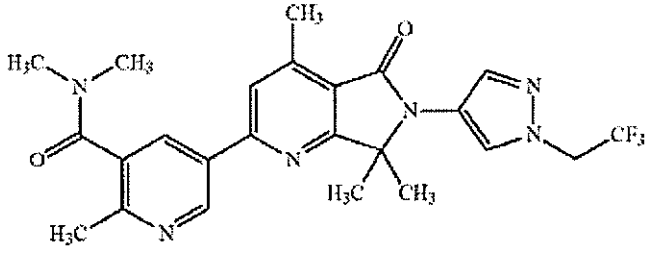

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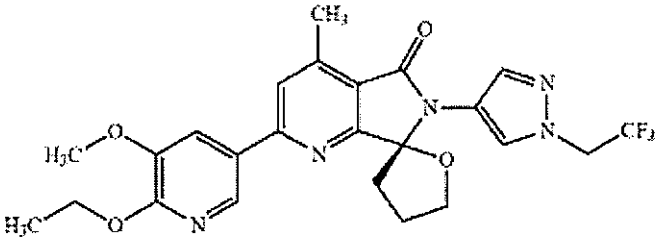

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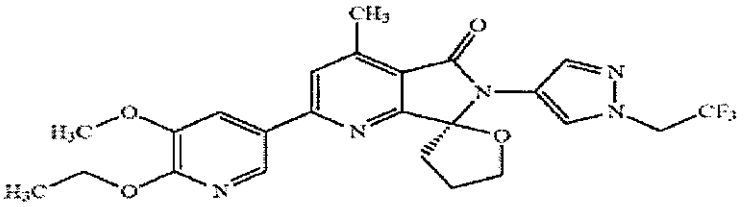

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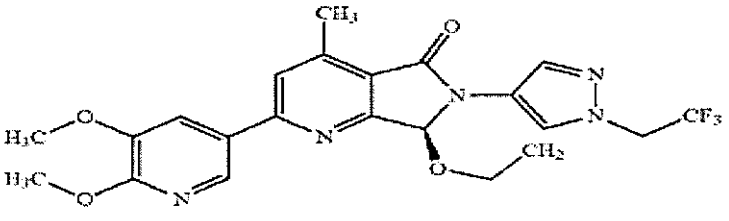

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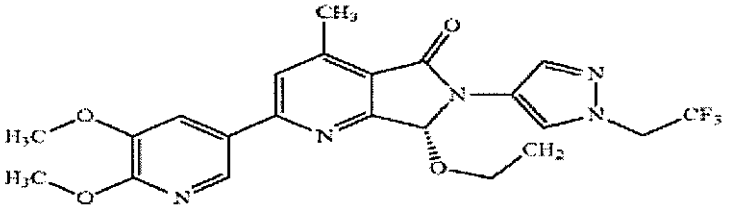

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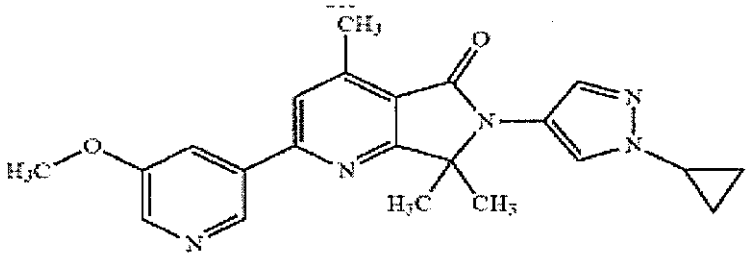

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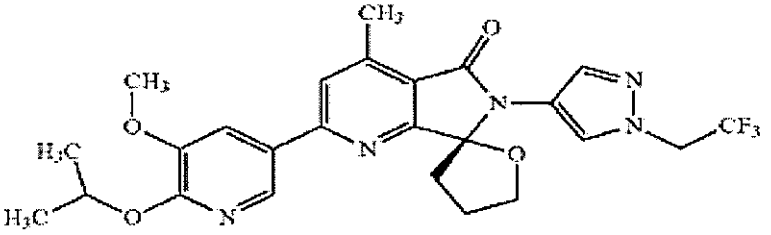

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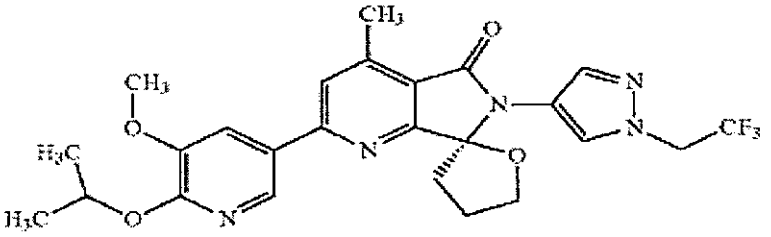

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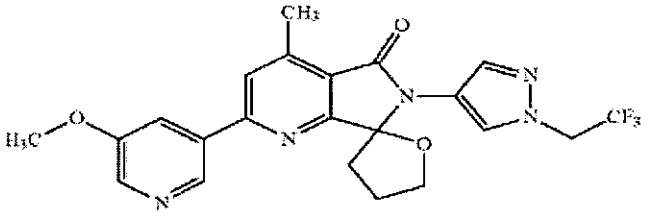

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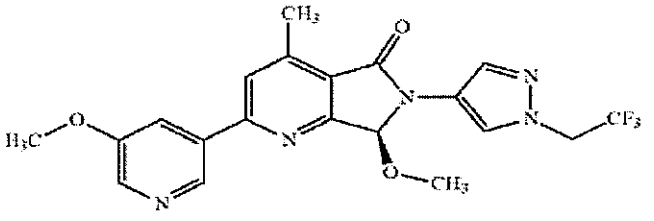

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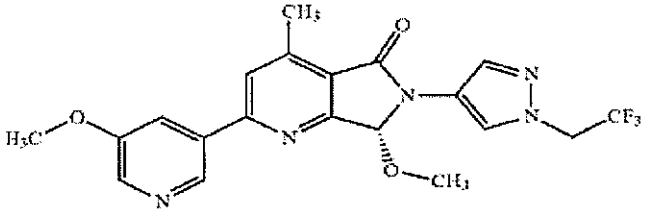

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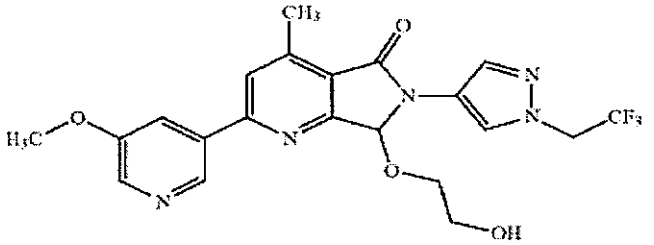

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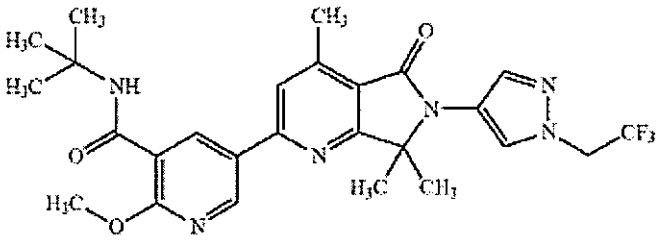

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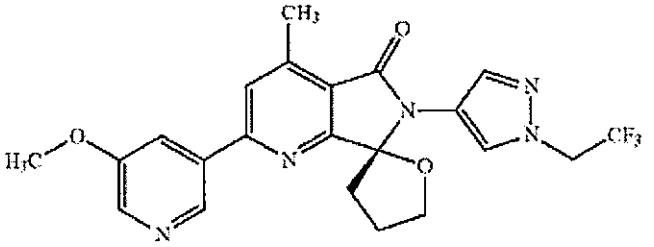

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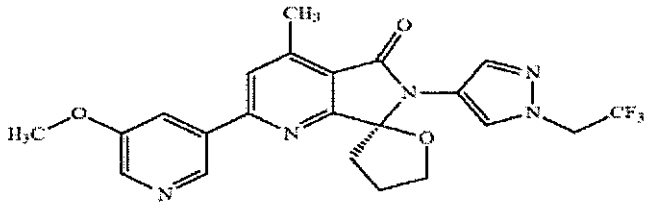

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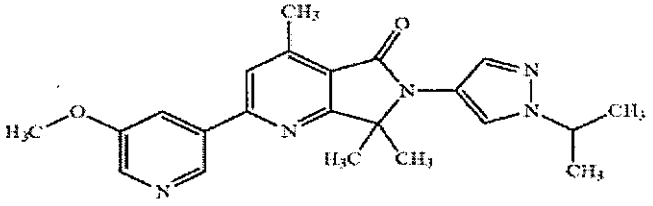

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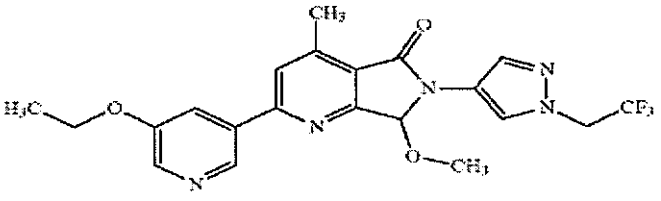

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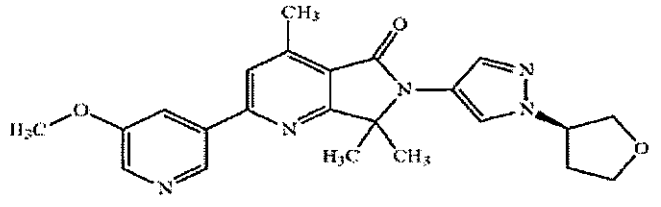

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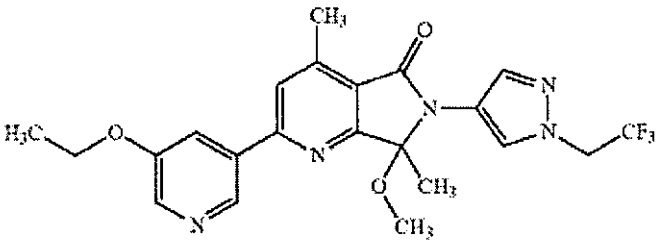

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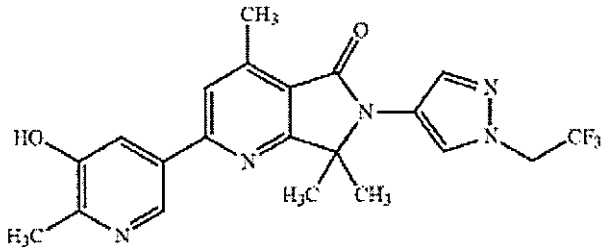

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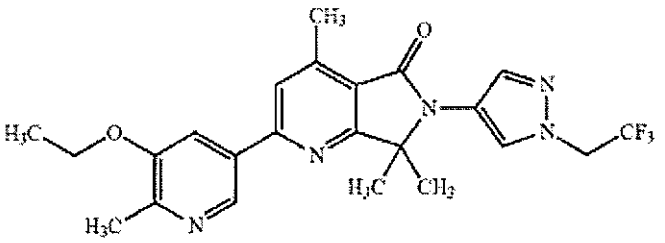

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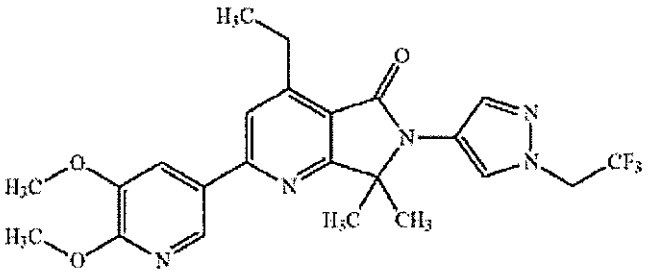

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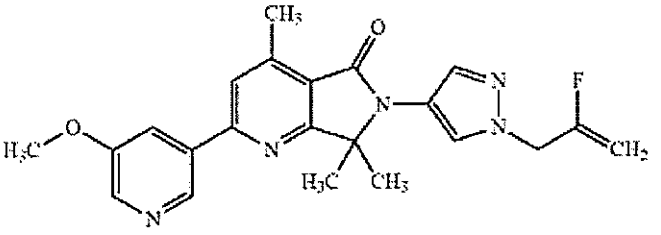

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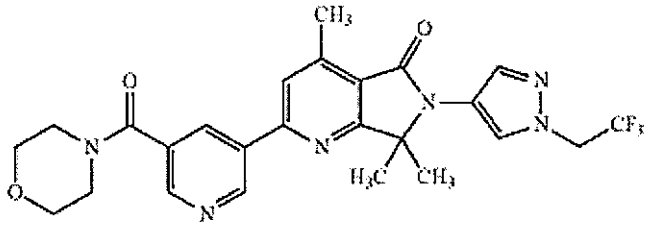

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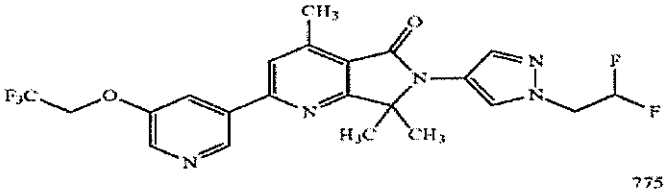

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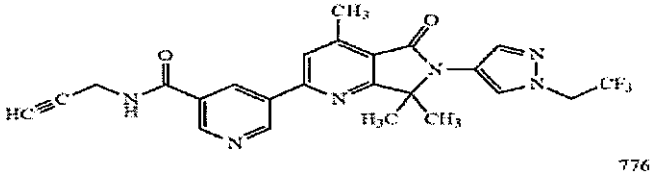

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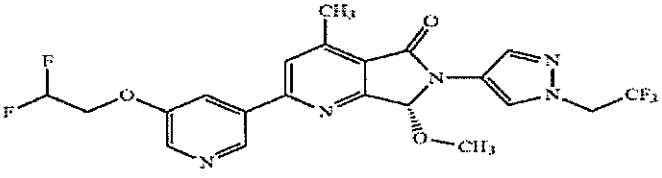

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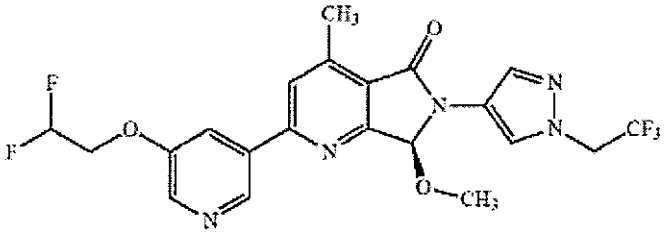

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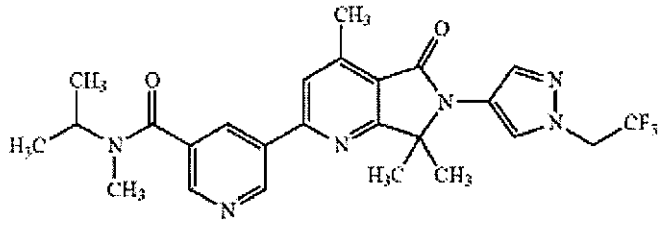

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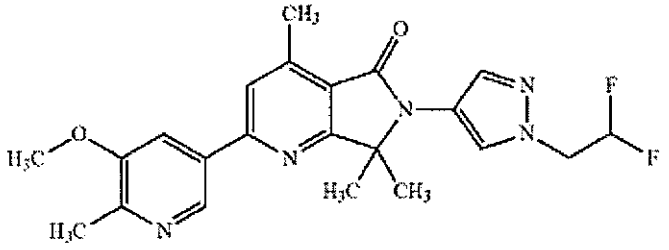

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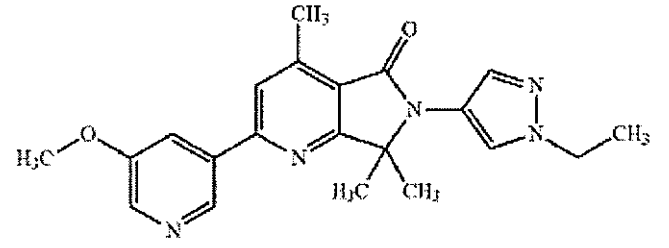

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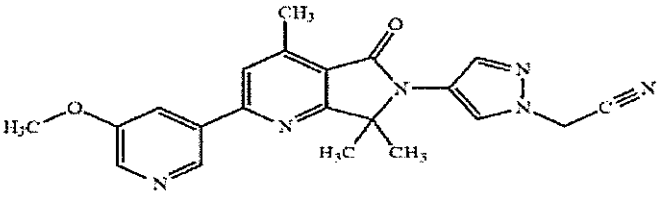

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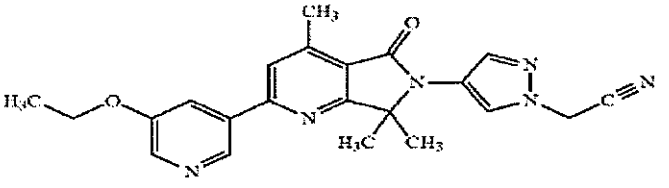

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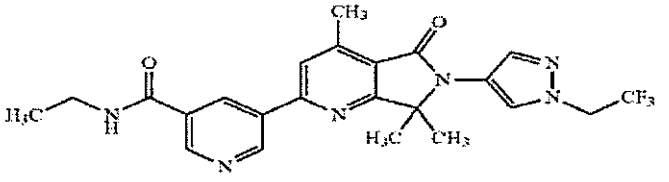

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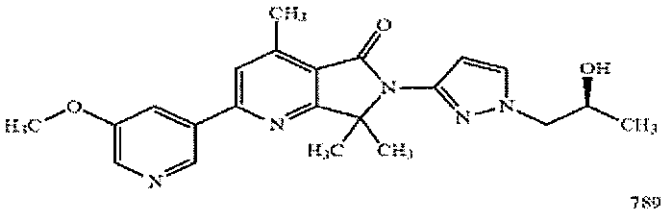

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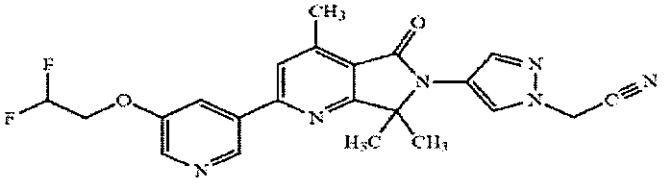

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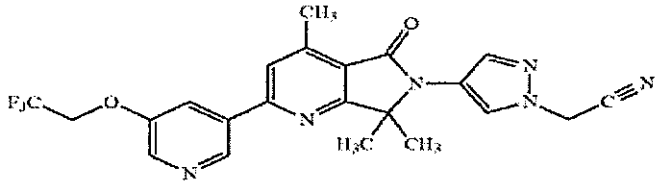

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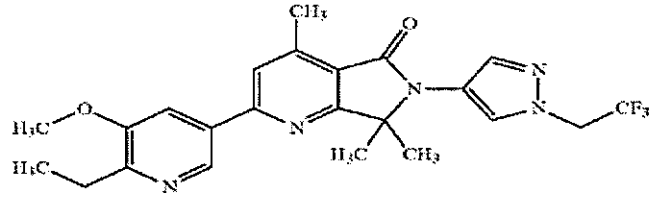

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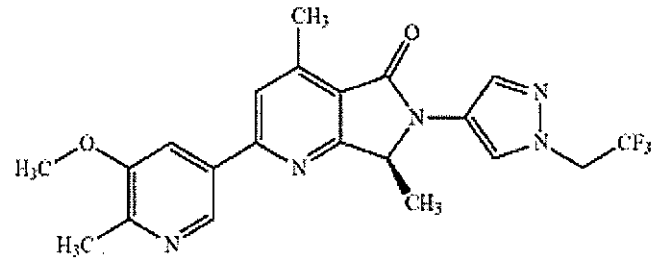

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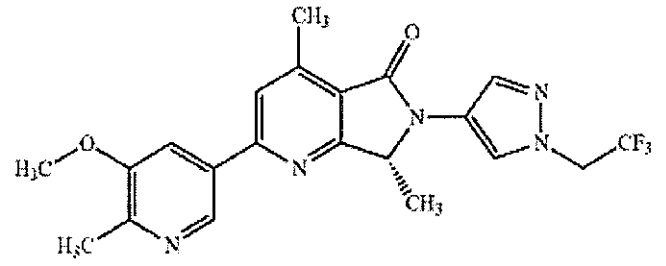

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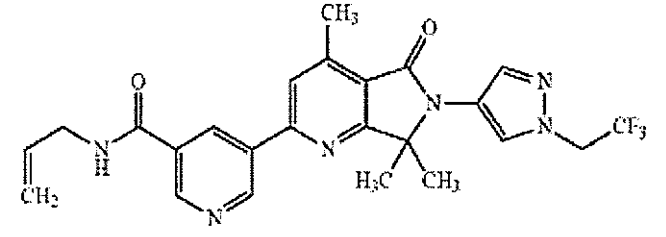

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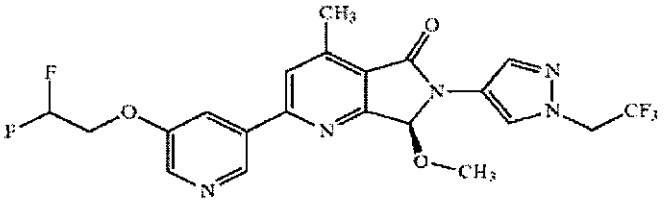

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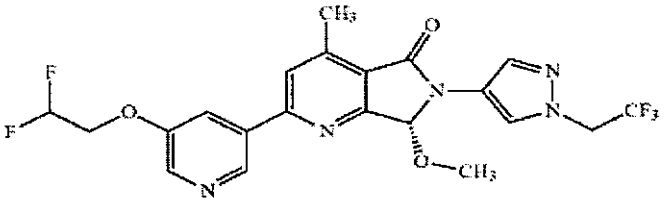

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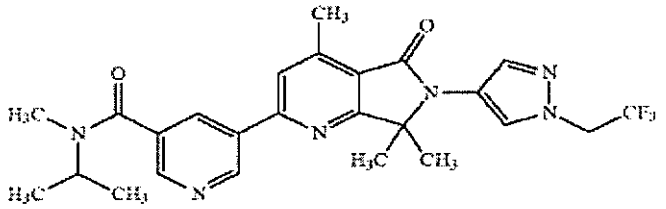

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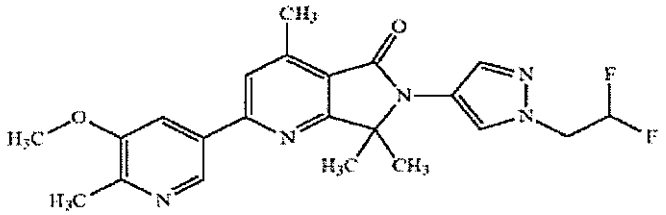

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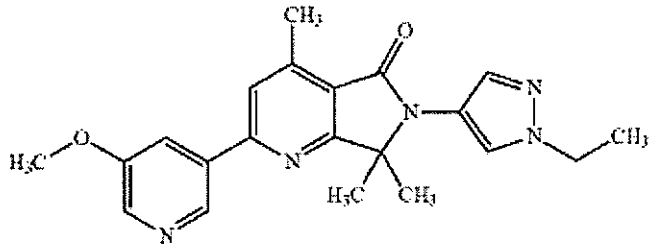

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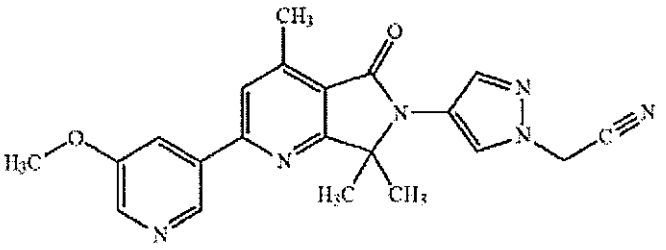

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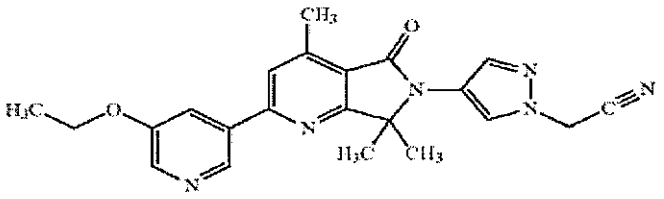

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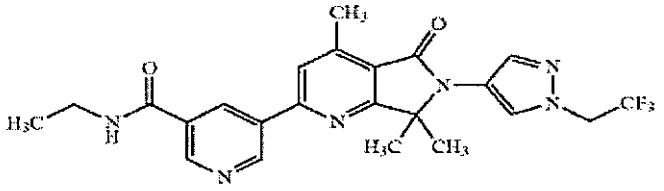

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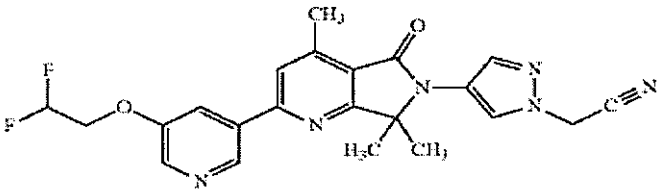

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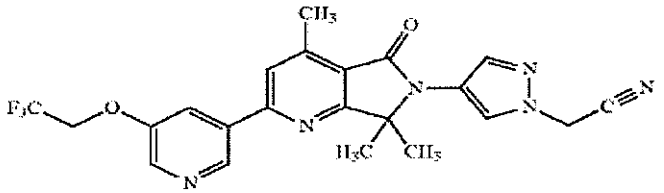

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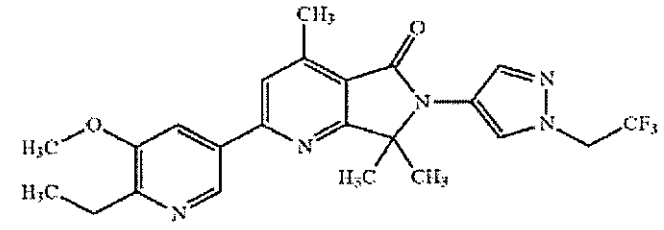

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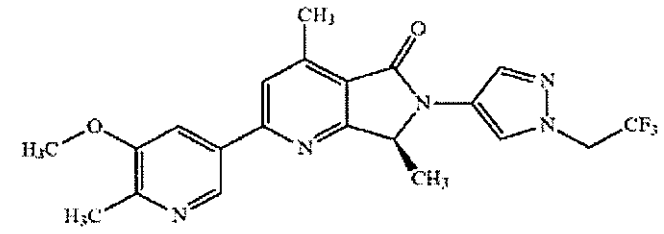

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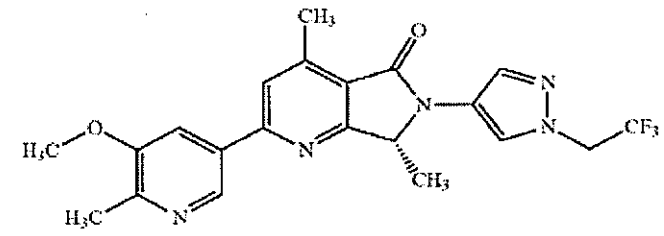

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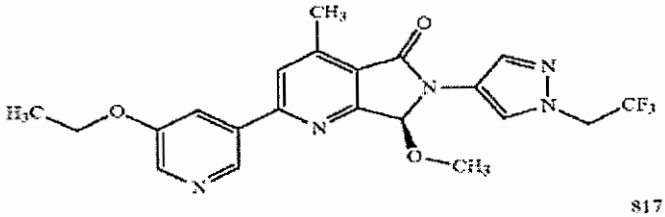

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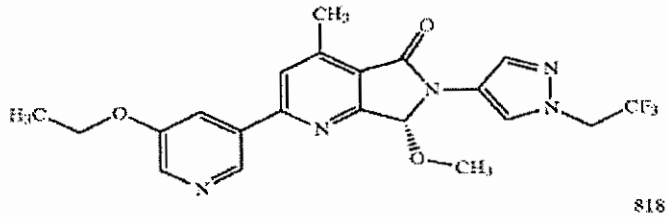

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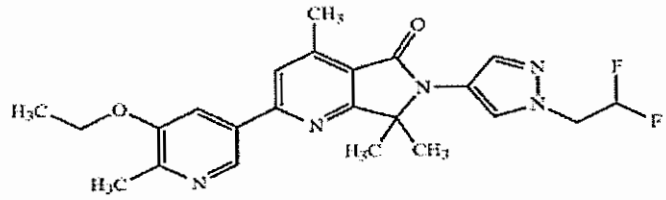

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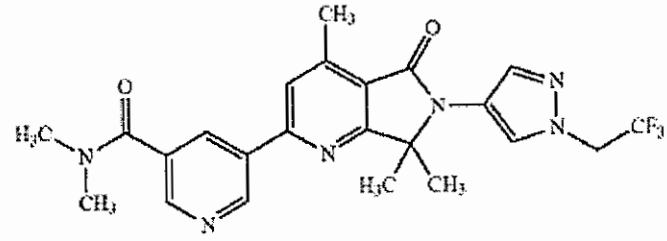

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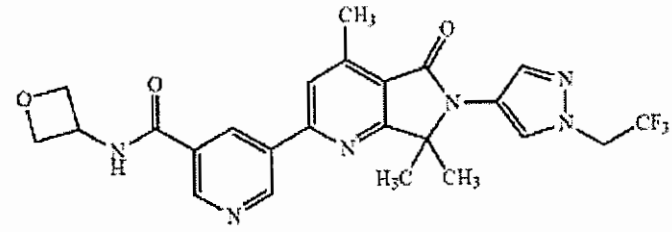

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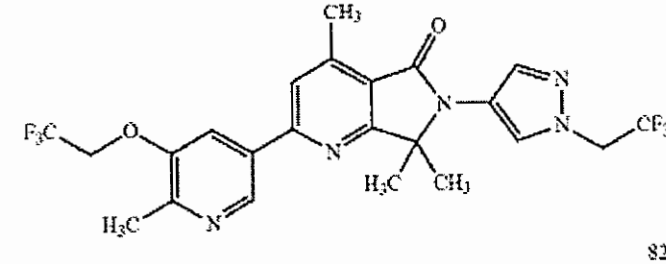

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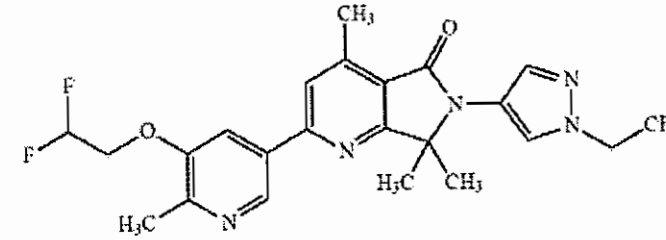

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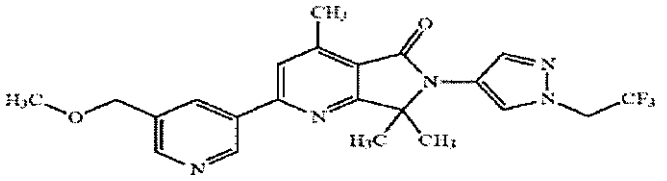

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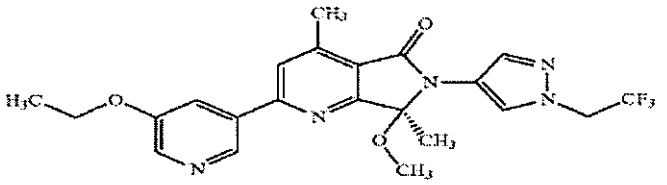

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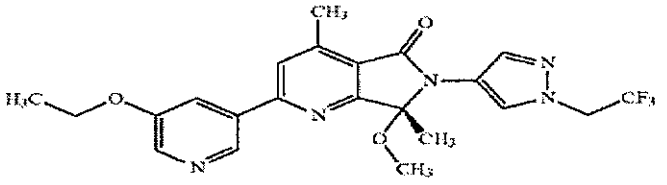

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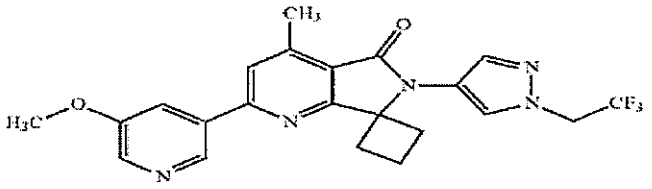

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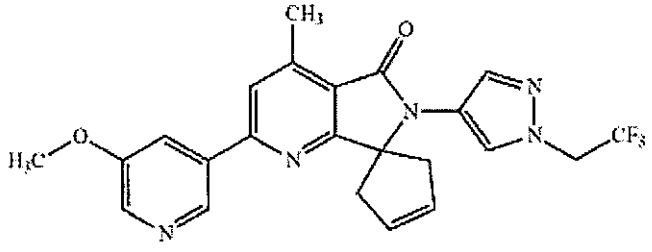

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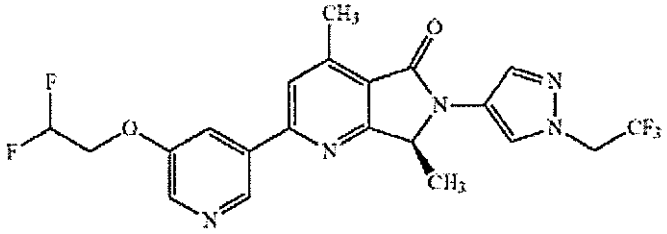

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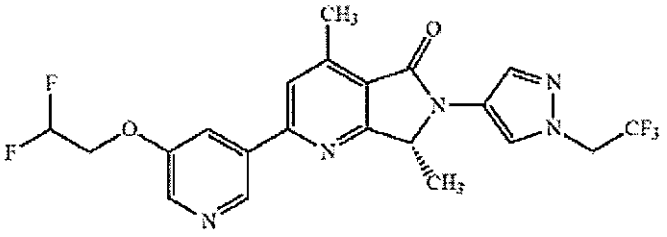

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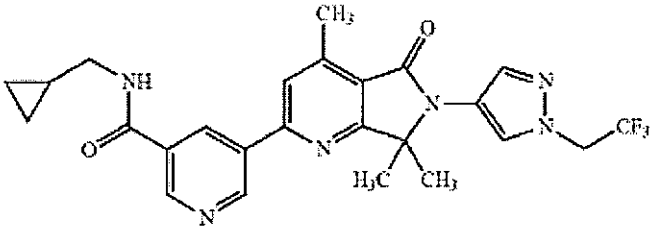

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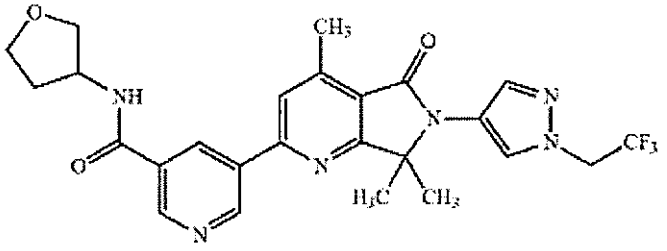

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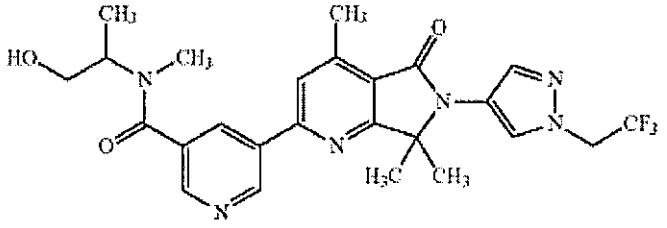

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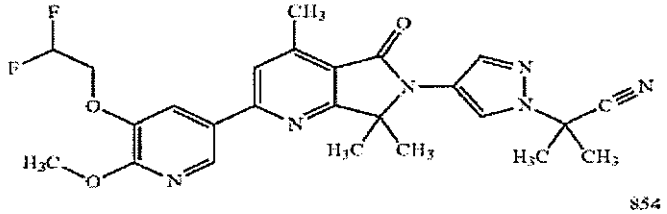

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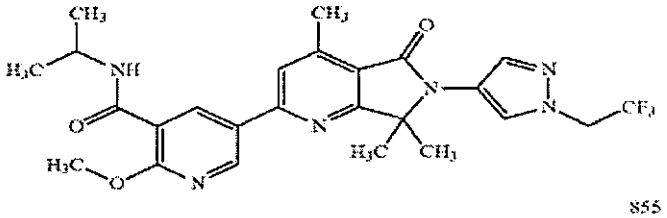

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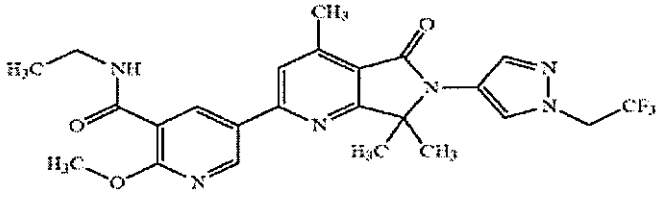

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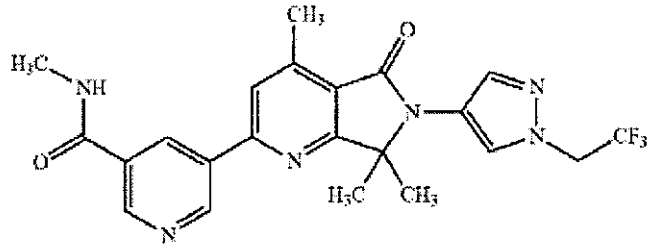

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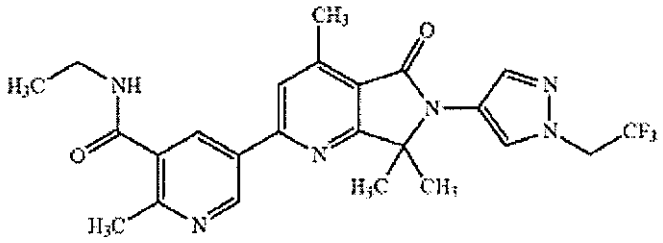

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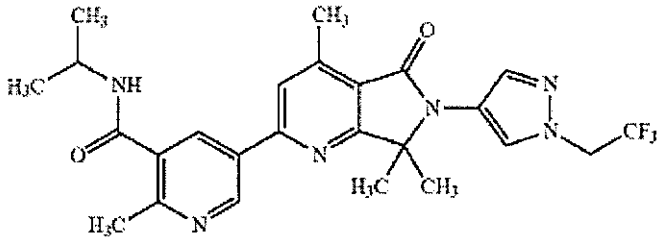

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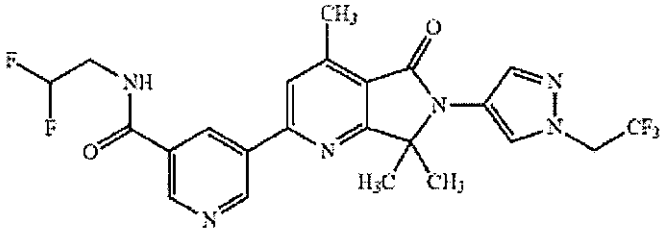

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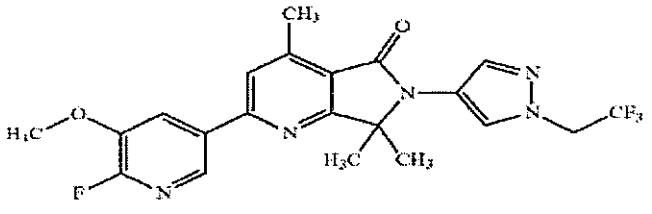

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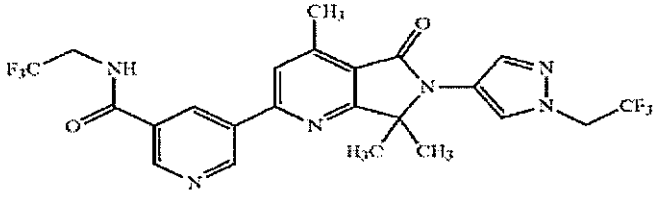

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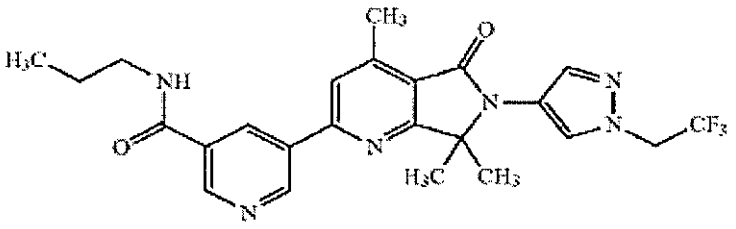

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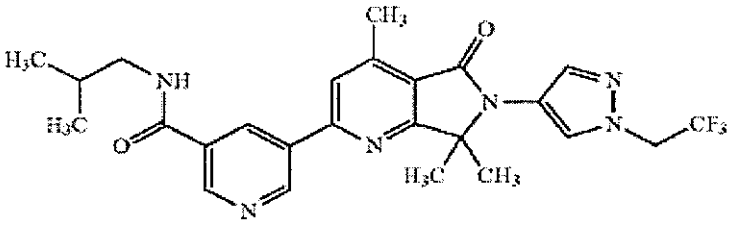

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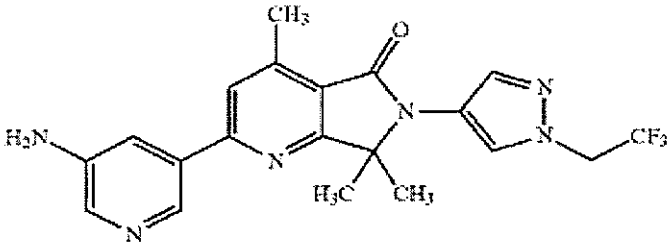

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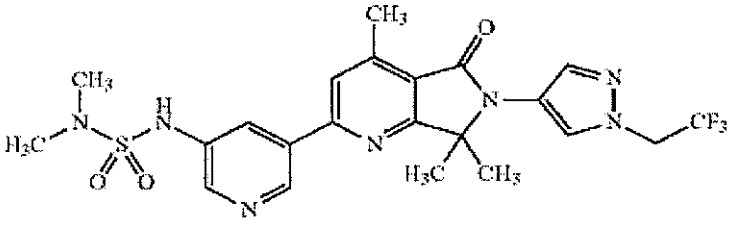

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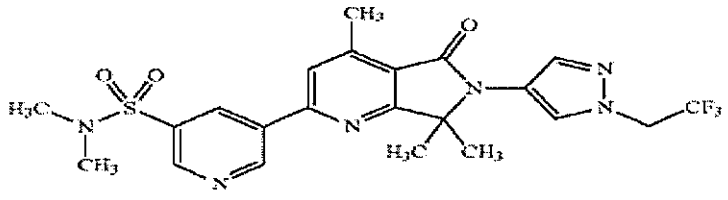

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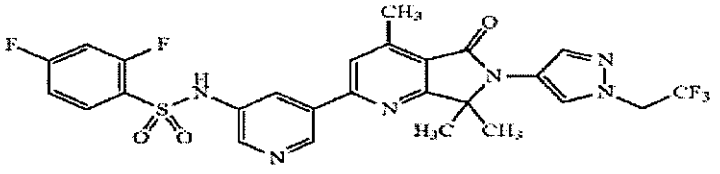

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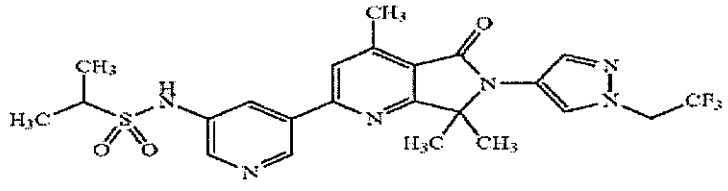

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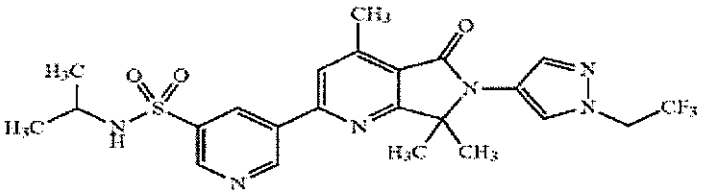

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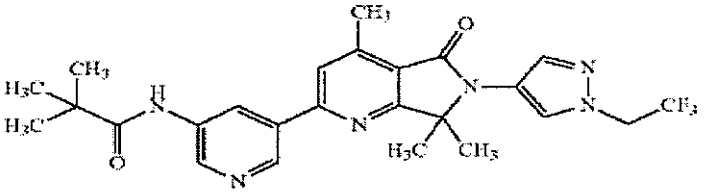

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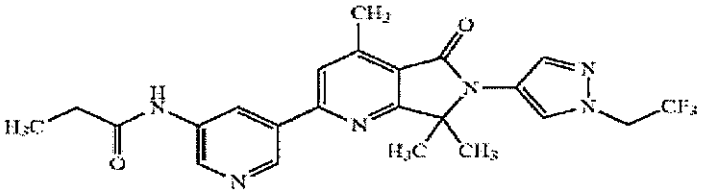

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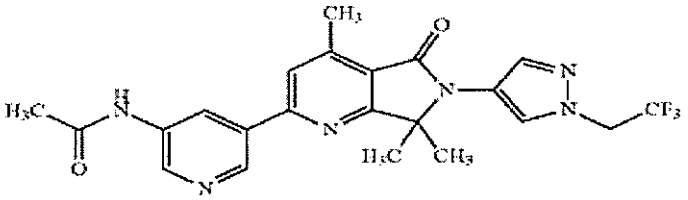

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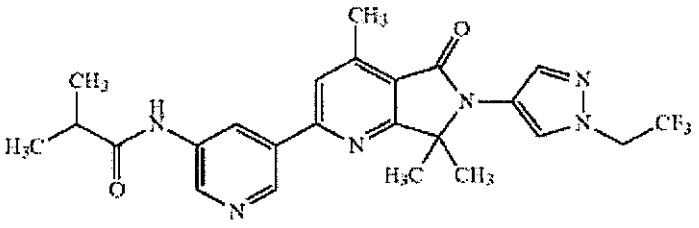

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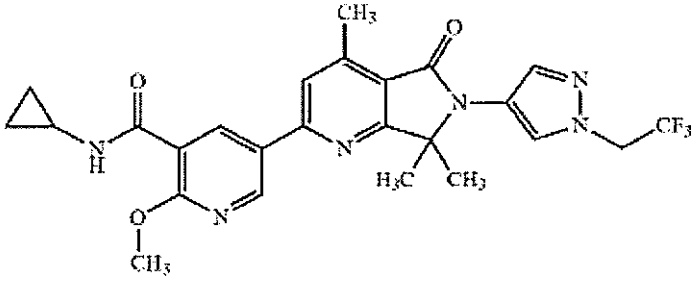

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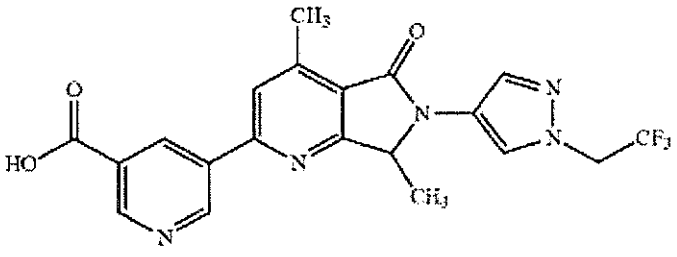

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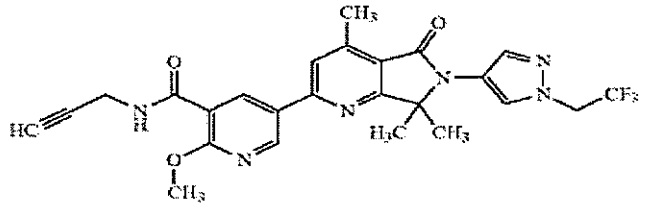

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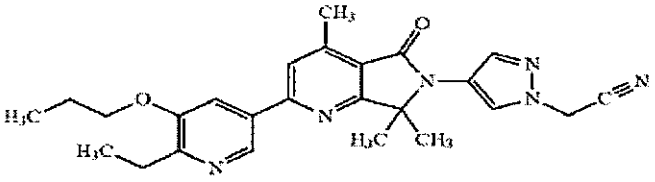

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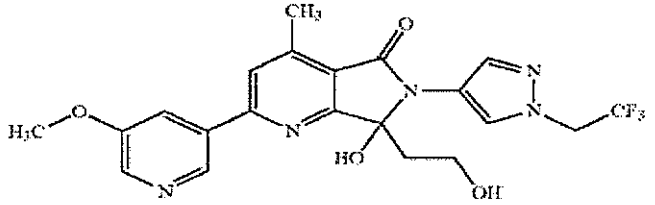

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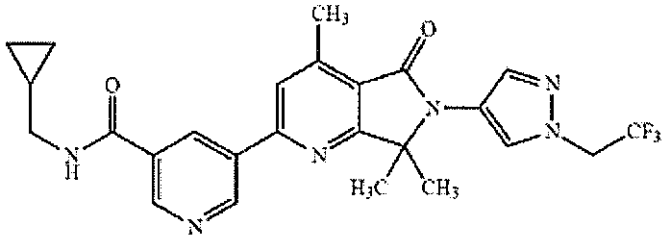

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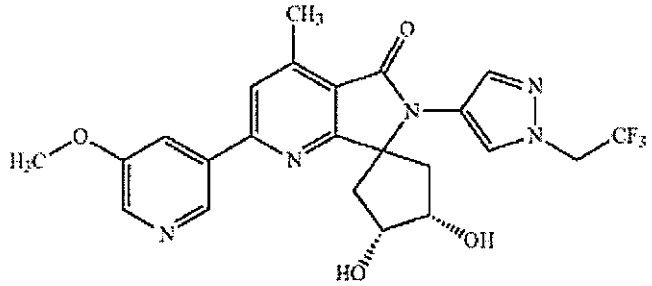

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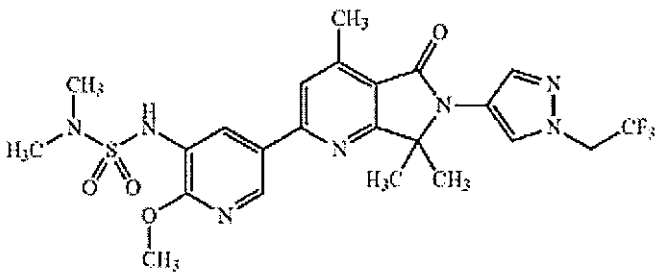

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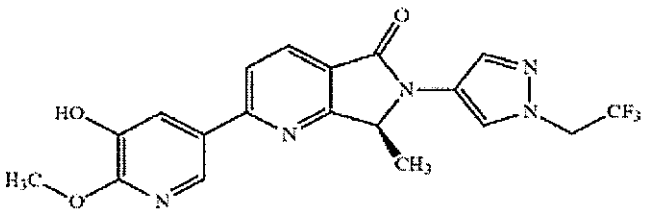

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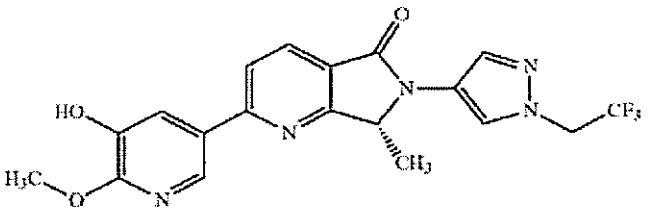

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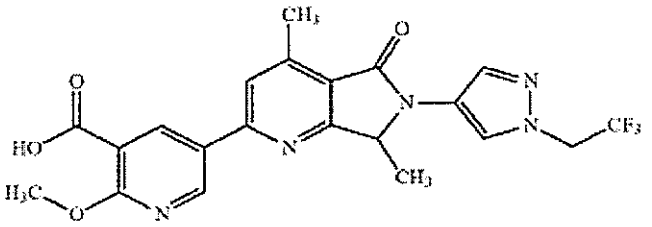

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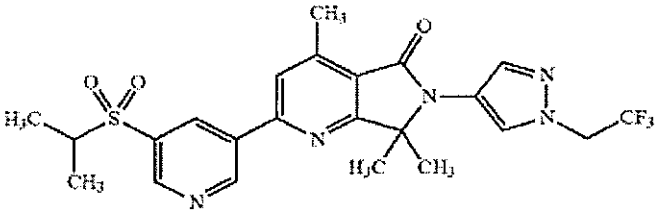

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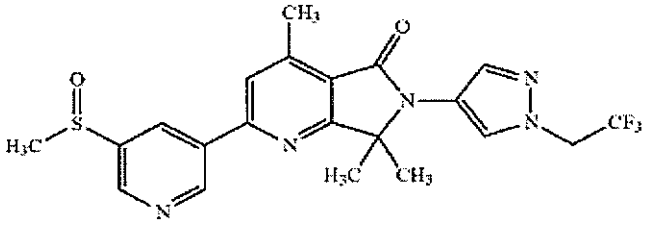

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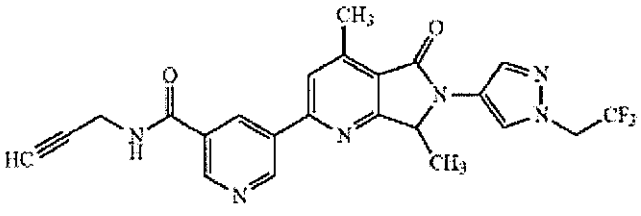

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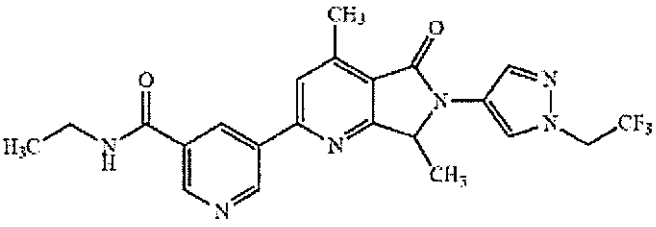

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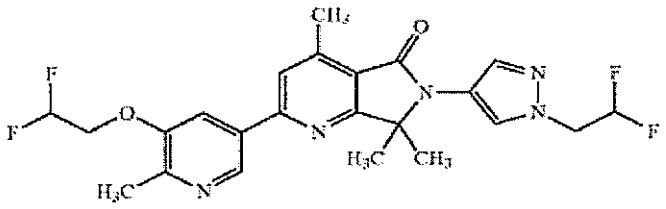

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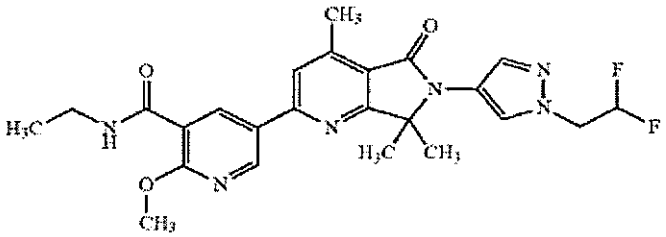

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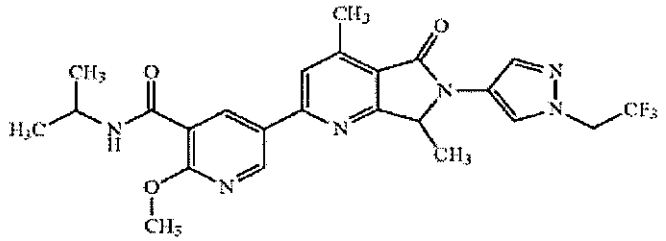

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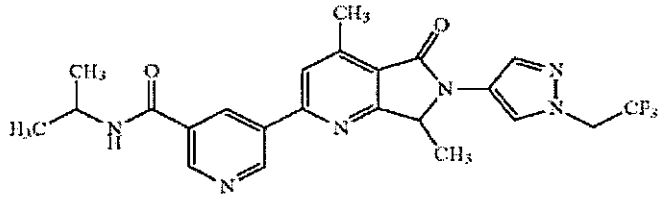

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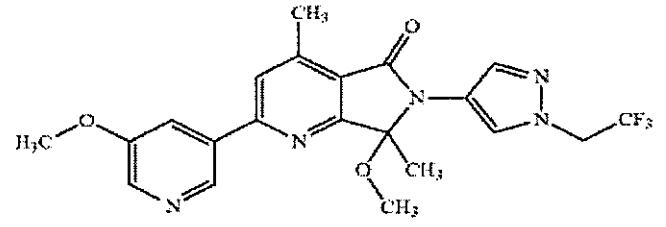

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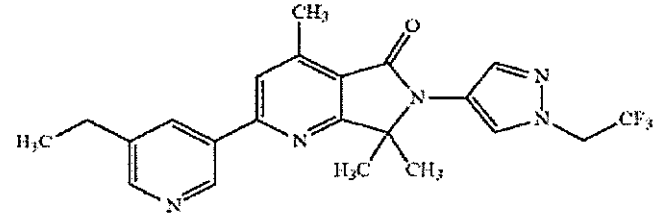

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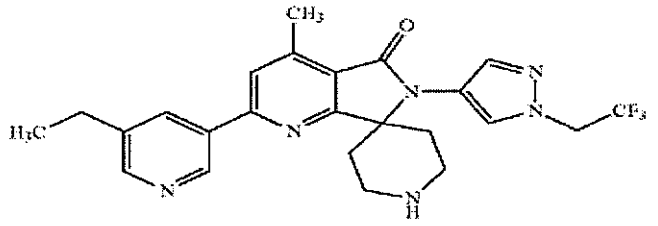

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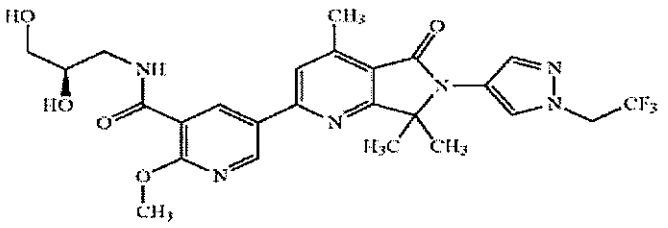

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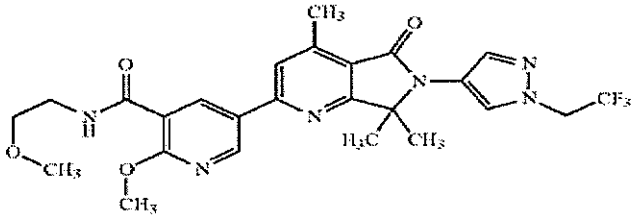

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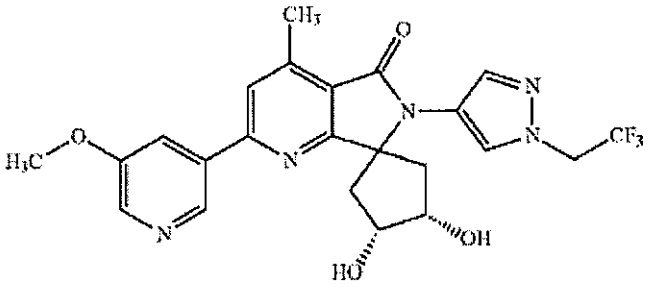

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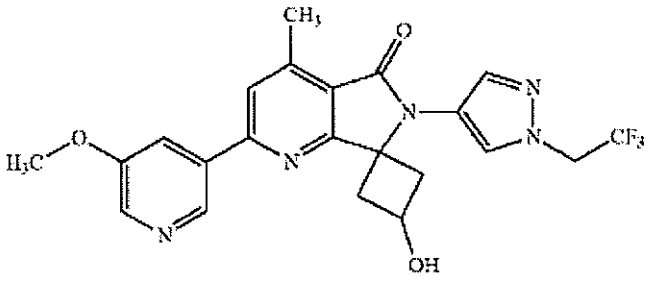

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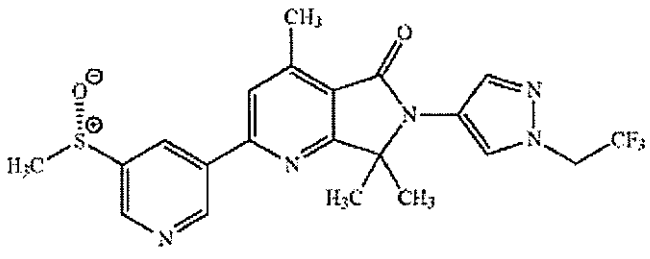

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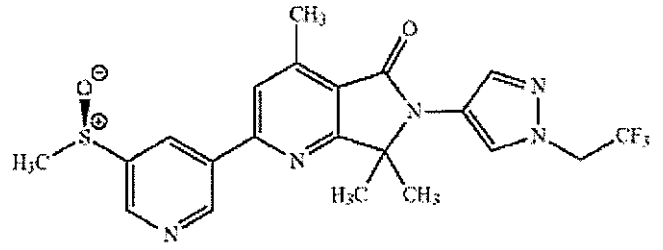

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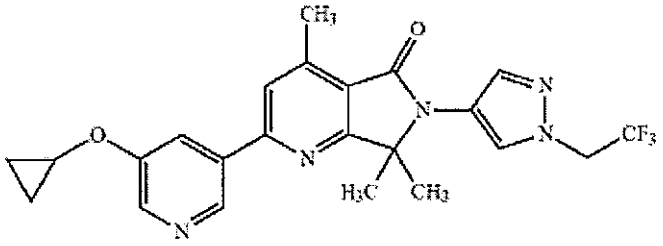

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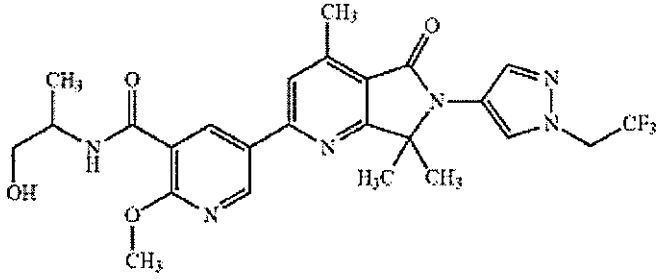

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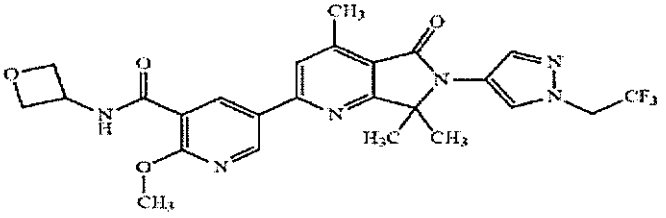

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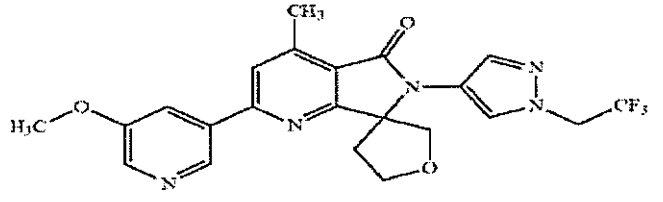

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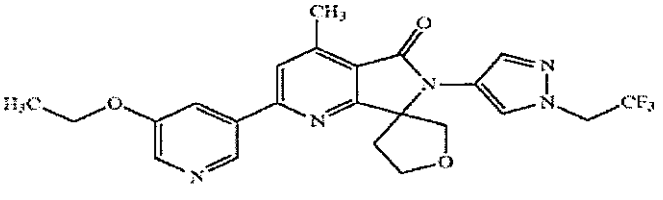

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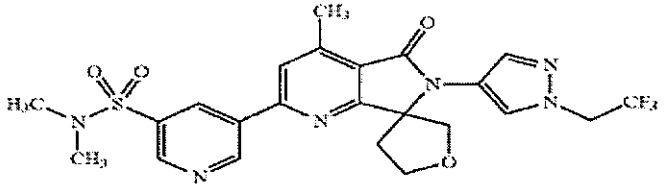

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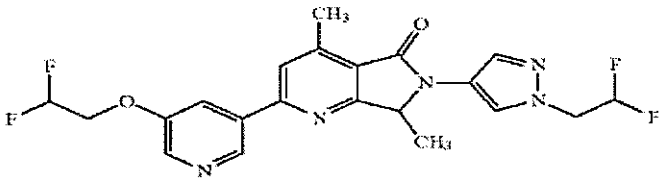

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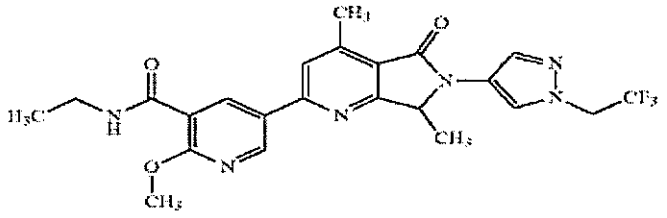

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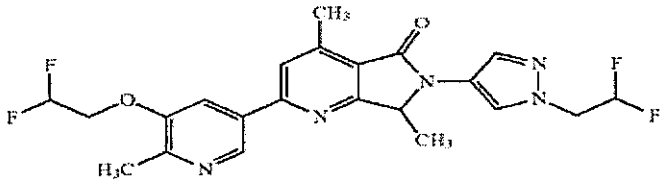

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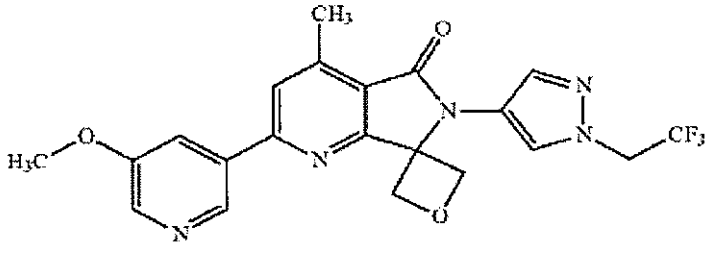

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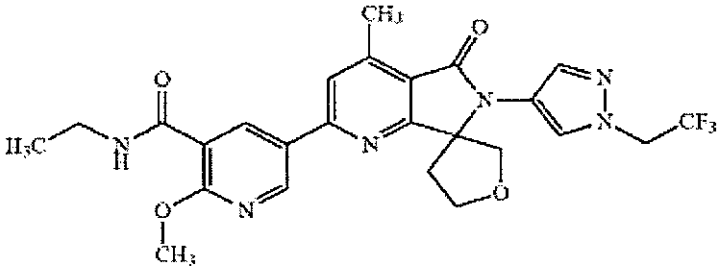

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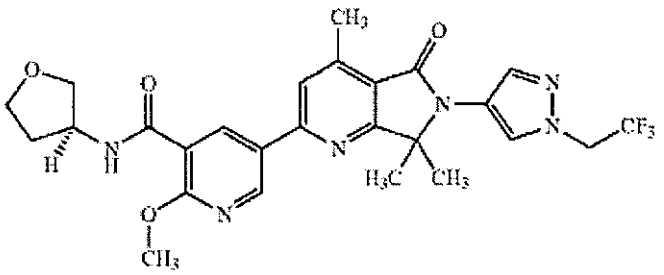

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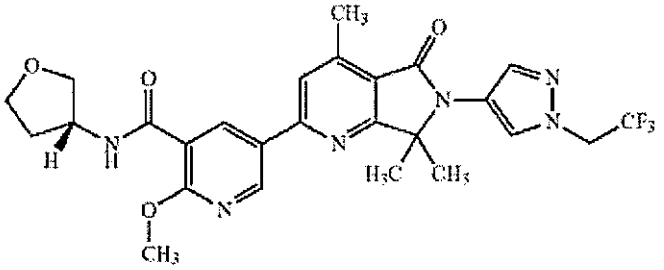

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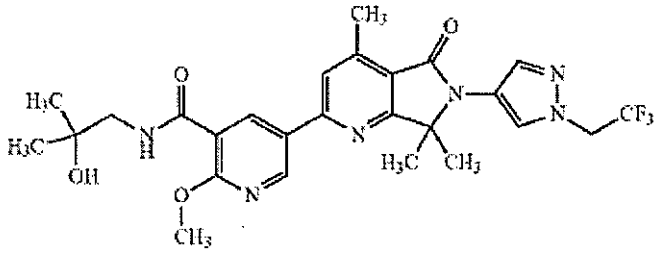

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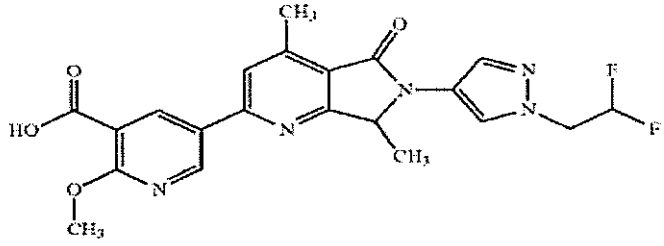

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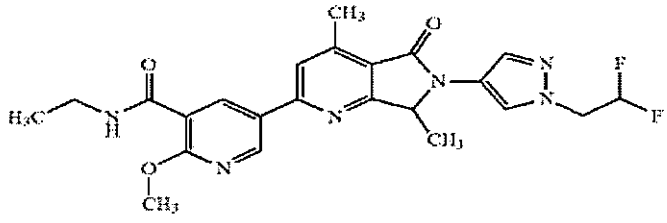

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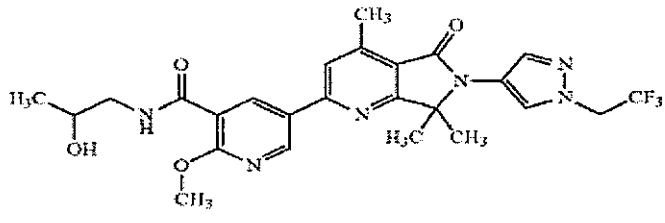

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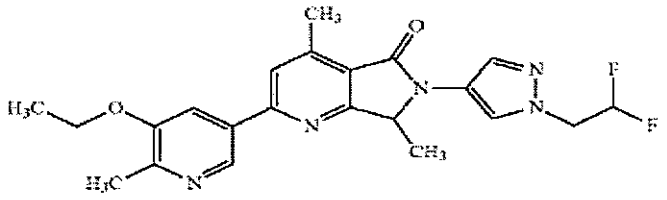

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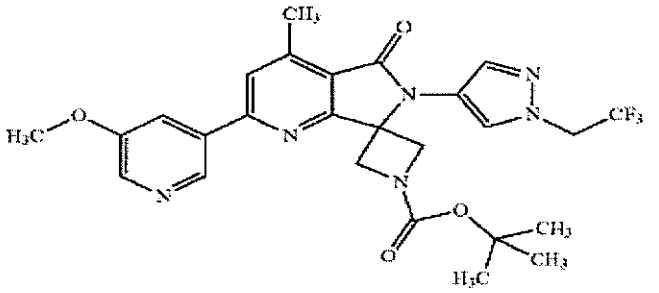

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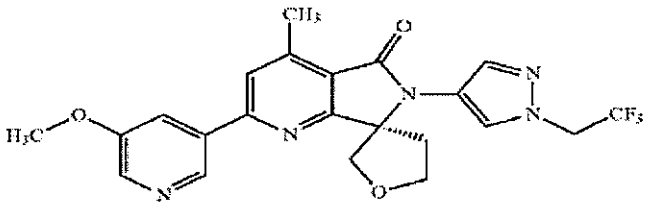

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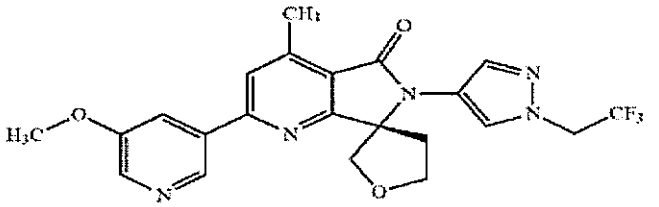

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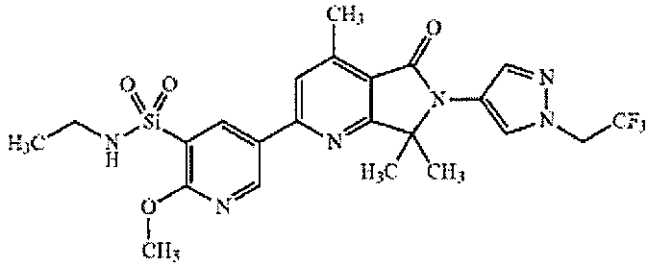

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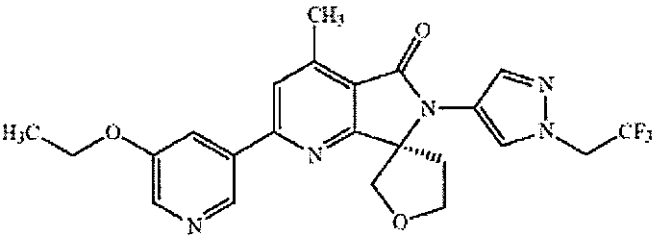

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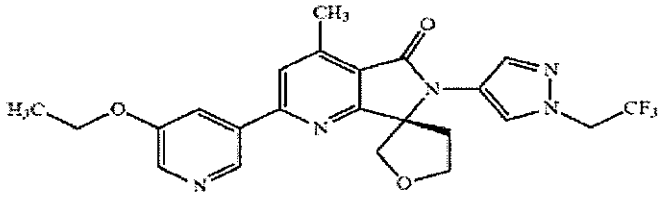

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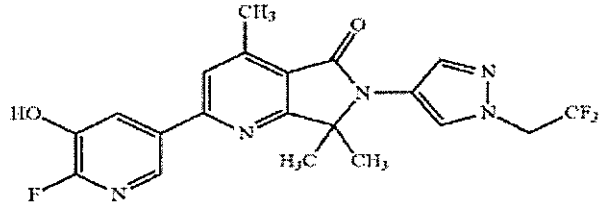

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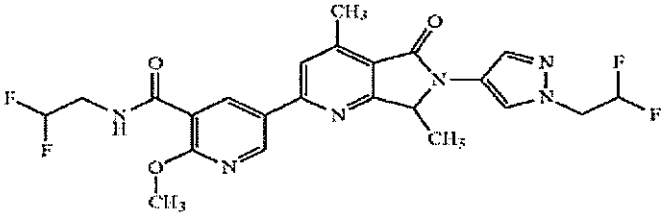

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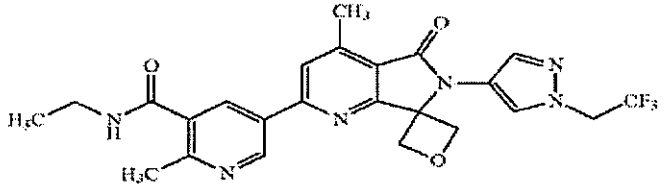

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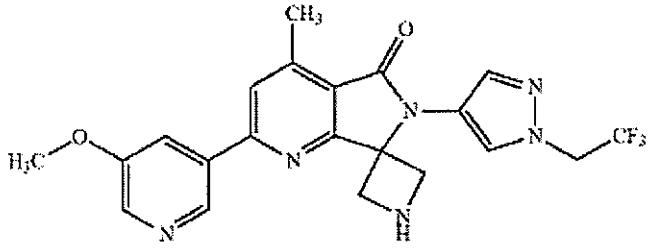

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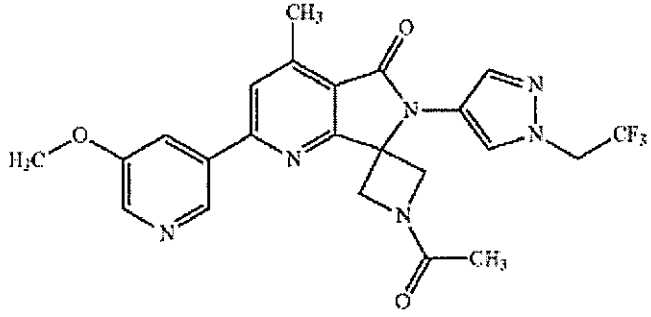

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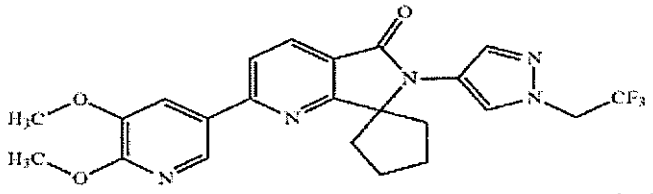

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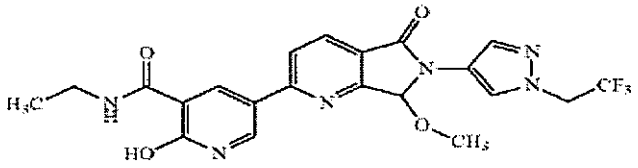

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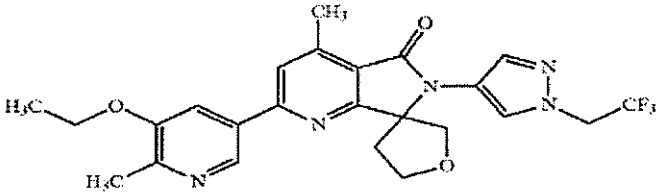

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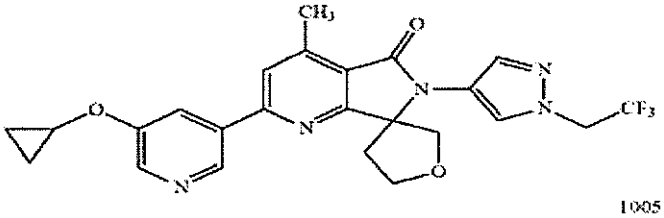

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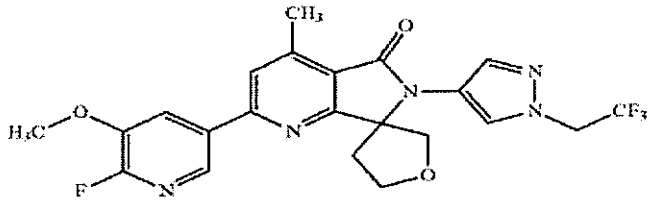

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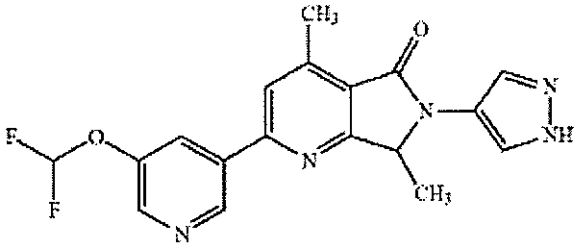

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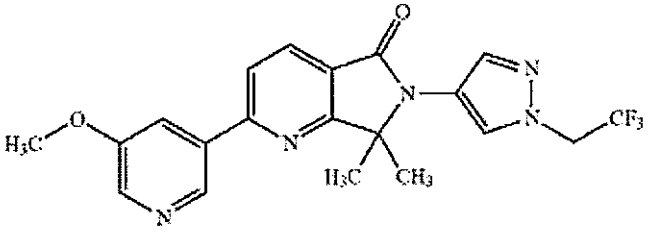

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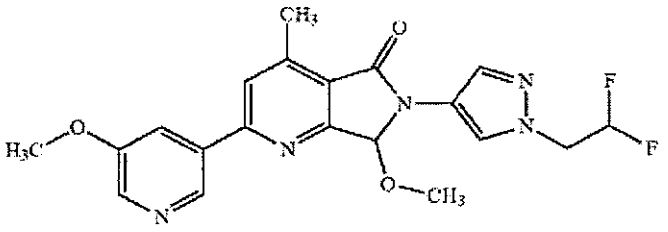

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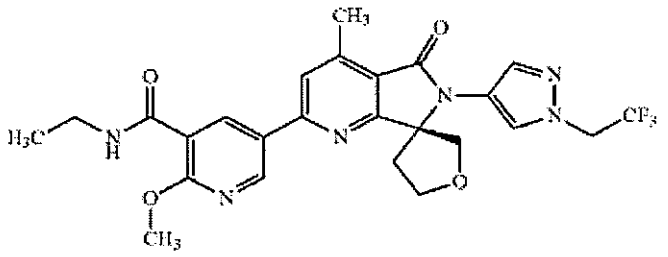

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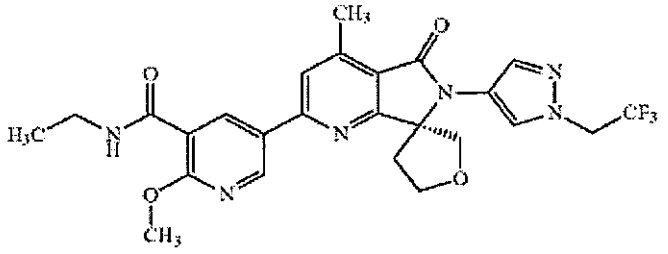

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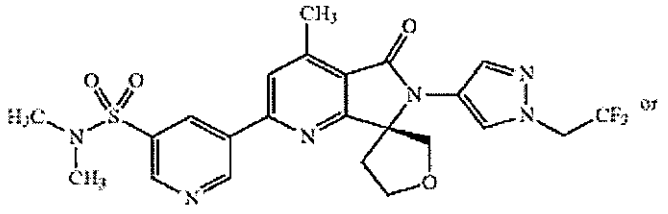

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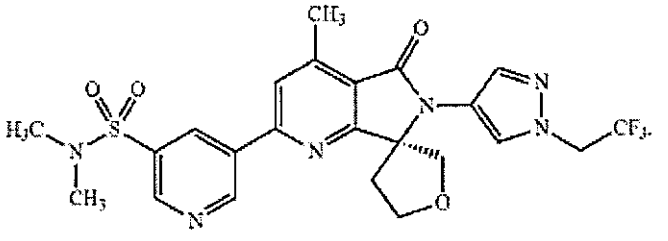

or a pharmaceutically acceptable salt thereof.

**17**. A pharmaceutical composition comprising a compound according to claim **1** or claim **4** and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

**18**. A method of inhibiting PI3K-gamma kinase activity in a biological sample comprising contacting said biological sample with a compound according to claim **1** or claim **4**, or a composition comprising said compound.