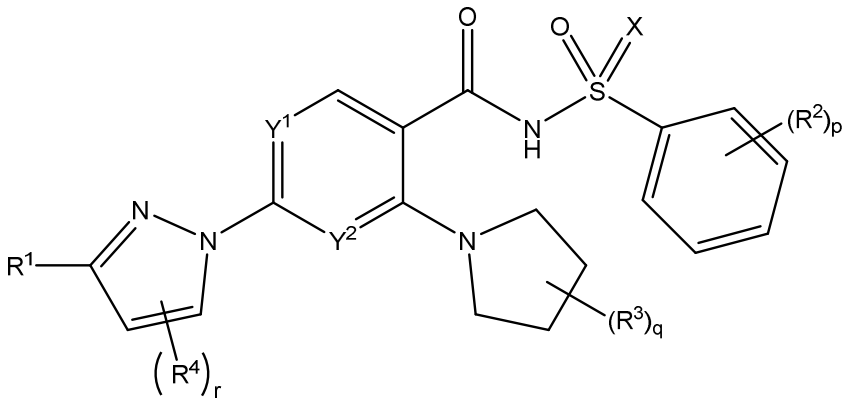
CLAIMS

1. A compound of Formula I:



(I),

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing,

wherein:

- one of Y^1 and Y^2 is N and the other is CH;

- **X** is chosen from O, NH, and N(C_1-C_4 alkyl) groups;

- $\mathbf{R^1}$ is chosen from $–(C\mathbf{R}_2)_k$-O-$(C\mathbf{R}_2)_m(C\mathbf{R})_n(\mathbf{Ring\ A})_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each $\mathbf{R^3}$ is independently chosen from C_1-C_2 alkyl groups optionally substituted with one or more OH groups;

- each $\mathbf{R^4}$ is independently chosen from halogens;

- k is 0 or 1;

- r is 0 or 1;

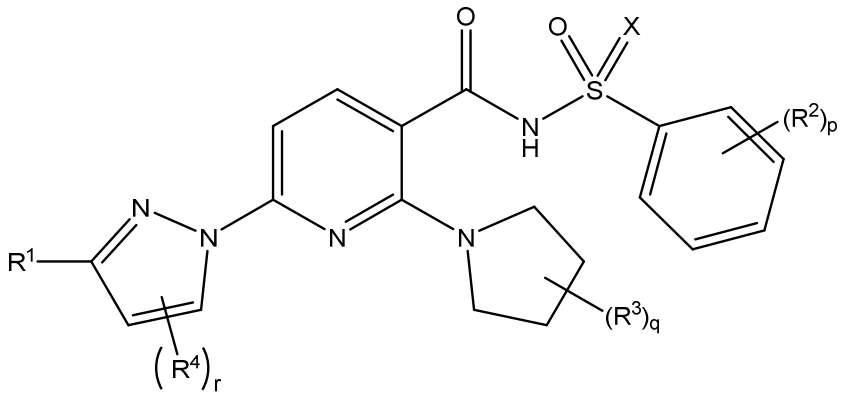
- m is 0, 1, 2, or 3;

- n is 0 or 1;

- p is 0, 1, 2, 3, 4, or 5; and

- q is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

2. A compound of claim 1, wherein the compound is of Formula II:



(II),

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing,

wherein:

- X is chosen from O, NH, and N(C_1-C_4 alkyl) groups;

- **R^1** is chosen from –(C**R**$_2$)$_k$-O-(C**R**$_2$)$_m$(C**R**)$_n$(**Ring A**)$_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each **R^2** is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each **R^3** is independently chosen from C_1-C_2 alkyl groups optionally substituted with one or more OH groups;

- each **R^4** is independently chosen from halogens;

- k is 0 or 1;

- r is 0 or 1;

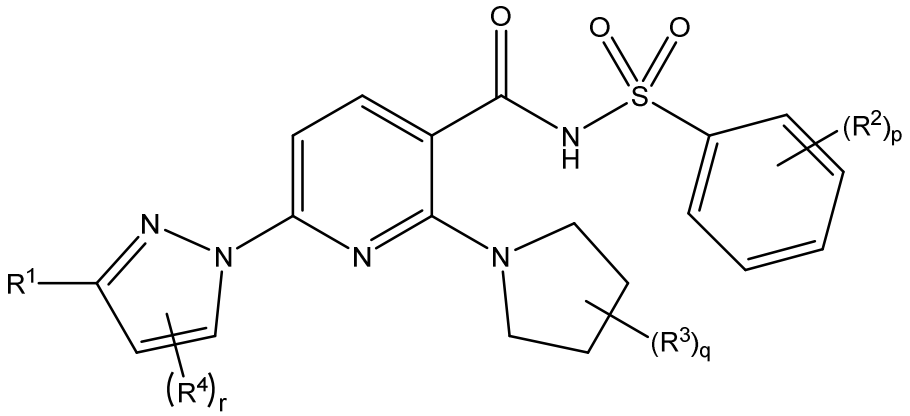
- m is 0, 1, 2, or 3;

- n is 0 or 1;

- p is 0, 1, 2, 3, 4, or 5; and

- q is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

3. A compound of claim 1, wherein the compound is of Formula III:



(III),

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein:

- $\mathbf{R^1}$ is chosen from $-(C\mathbf{R}_2)_k\text{-}O\text{–}(C\mathbf{R}_2)_m(C\mathbf{R})_n(\mathbf{Ring\ A})_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each $\mathbf{R^3}$ is independently chosen from C_1-C_2 alkyl groups optionally substituted with one or more OH groups;

- each $\mathbf{R^4}$ is independently chosen from halogens;

- k is 0 or 1;

- r is 0 or 1;

- m is 0, 1, 2, or 3;

- n is 0 or 1;

- p is 0, 1, 2, 3, 4, or 5; and

- q is 0, 1, 2, 3, 4, 5, 6, 7, or 8.

4. A compound according to any of claims 1-3, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein if $\mathbf{R^2}$ is cyano, then said $\mathbf{R^2}$ is *meta* or *para* relative to the sulfur atom.

5. A compound according to any of claims 1-3, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein:

- each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

- each **R** is independently chosen from H and OH;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, and halogens;

- $\mathbf{R^4}$ is F;

- k is 0;

- p is 0, 1, or 2;

- q is 0, 1, 2, 3, or 4;

- r is 0; and

wherein m and n are not 0 at the same time.

6. A compound according to claim 5, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein:

- $\mathbf{R^1}$ is chosen from -O–(C$\mathbf{R}_2$)$_m$-**Ring A** groups,

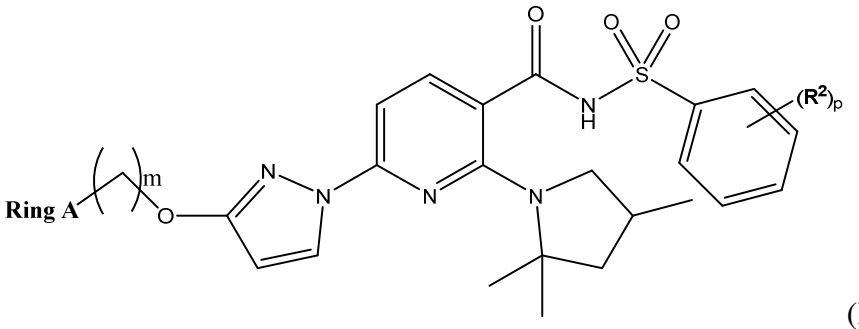
wherein **Ring A** is chosen from C_3-C_{10} cycloalkyl groups

groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

- m is 1 or 2.

7. A compound according to claim 6, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein each $\mathbf{R^3}$ is a methyl group and q is 3 or 4.

8. A compound according to claim 7 having Formula IV:



(IV),

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing,

wherein:

- **Ring A** is chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens; and

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, F, Cl, and C_1-C_2 alkoxy groups;

- m is 1 or 2; and

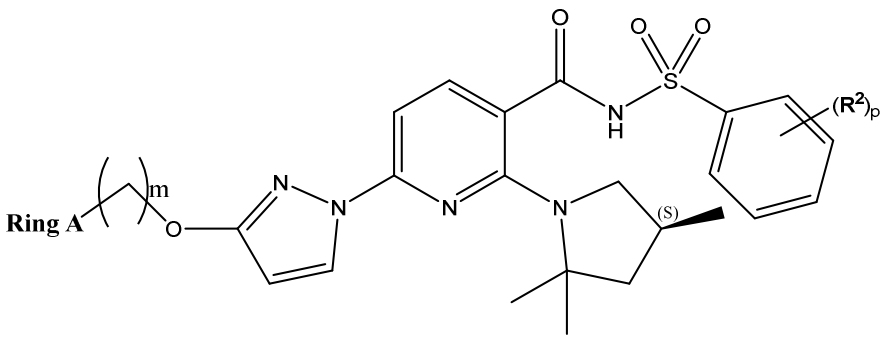
- p is 0, 1, or 2.

9. A compound according to claim 8, wherein:

(a) p is 0 or 1; or

(b) p is 0.

10. A compound according to claim 8 having Formula V:



(V),

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing,

wherein:

- **Ring A** is chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens; and

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, F, Cl, and C_1-C_2 alkoxy groups;

- m is 1 or 2; and

- p is 0, 1, or 2.

11. A compound according to any one of claims 1-10, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein each $\mathbf{R^2}$ is independently chosen from CH_3, OH, F, and OCH_3.

12. A compound according to claim 11, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein:

(a) p is 0 or 1; or

(b) p is 0.

13. A compound according to claim 10, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, wherein:

(a) **Ring A** is a cyclopropyl group substituted with a halogenated C_1 alkyl group or a halogenated C_2 alkyl group; or

(b) **Ring A** is a cyclopropyl group substituted with a CF_3 group; or

(c) m is 1, **Ring A** is a cyclopropyl group substituted with a CF_3 group, p is 0 or 1, and $\mathbf{R^2}$, if present, is a methyl group, a hydroxy group, or a methoxy group; or

(d) m is 2, **Ring A** is a C_3 cycloalkyl group substituted with a CF_3 group, p is 0 or 1, and $\mathbf{R^2}$, if present, is a methyl group, a hydroxy group, or a methoxy group; or

(e) m is 2, **Ring A** is a cyclopropyl group substituted with a CF_3 group, and p is 0; or

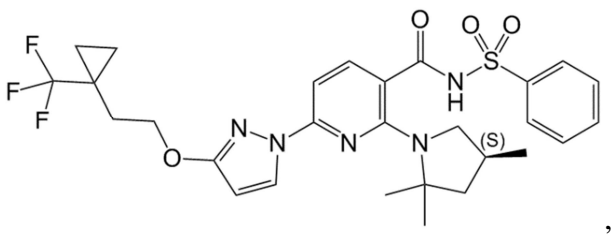
(f) **Ring A** is chosen from C_5 bicycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens; or

(g) **Ring A** is a C_5 bicycloalkyl group optionally substituted with a halogen; or

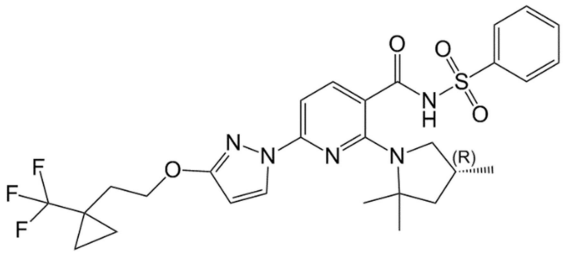
(h) **Ring A** is chosen from C_7 bicycloalkyl groups and C_7 tricycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens; or

(i) **Ring A** is an unsubstituted C_7 tricycloalkyl group.

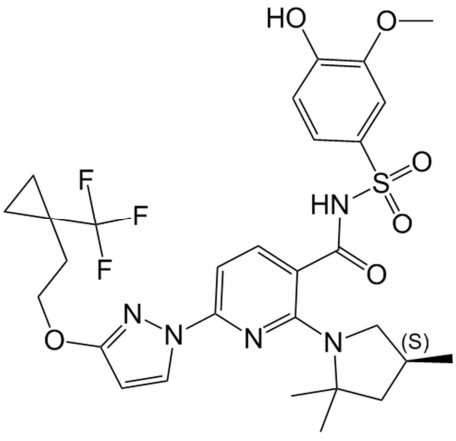
14. A compound according to claim 1 having a formula chosen from any one of the formulae depicted below:



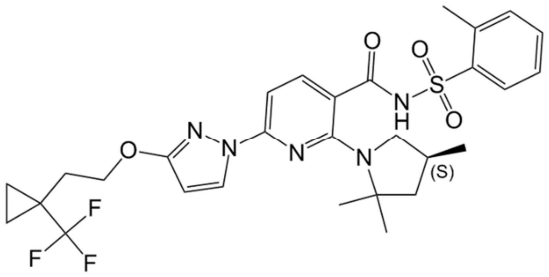
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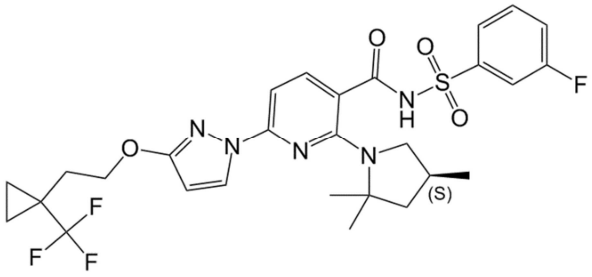


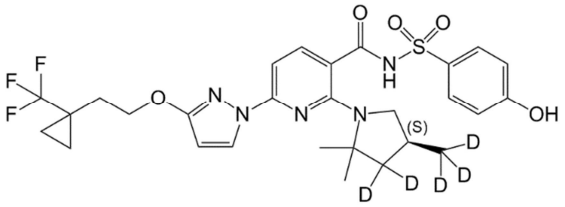
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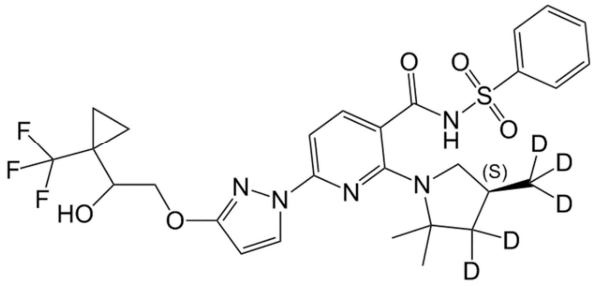


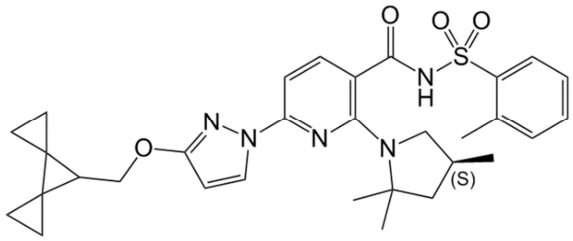
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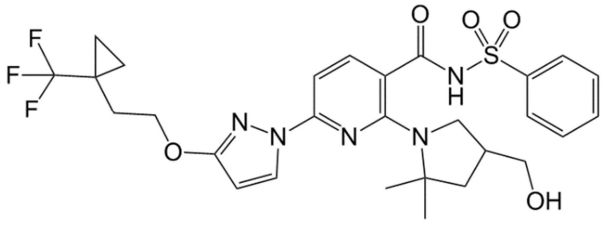

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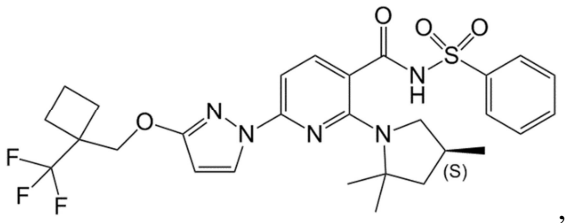

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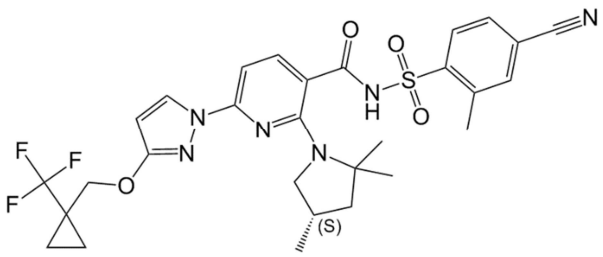

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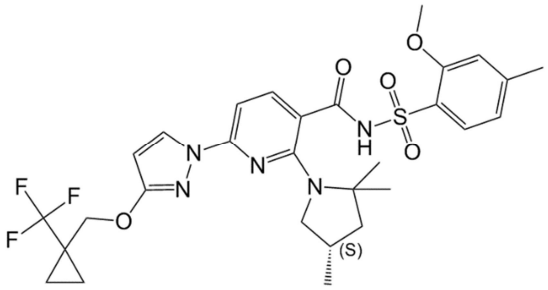

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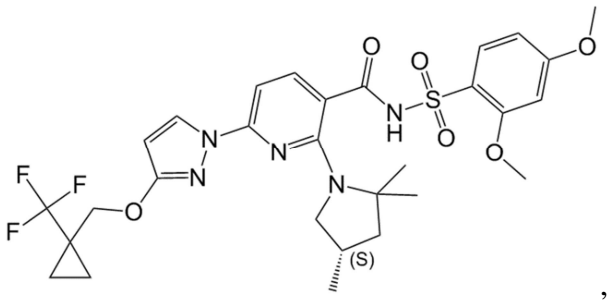

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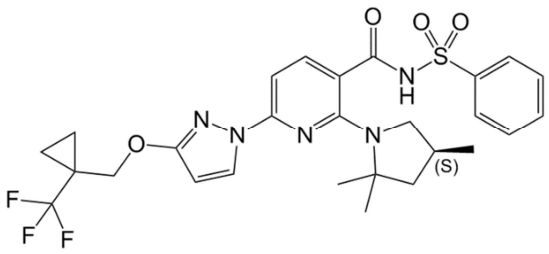

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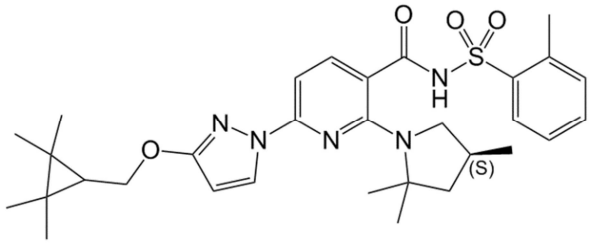

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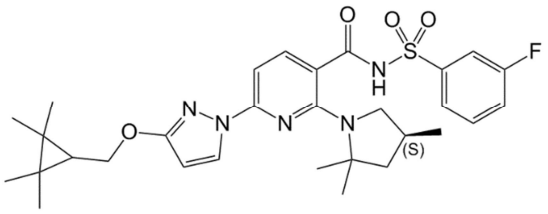

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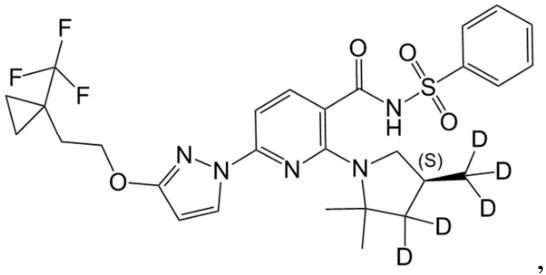

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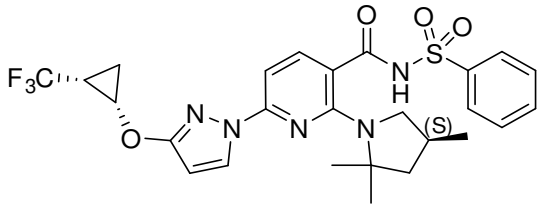

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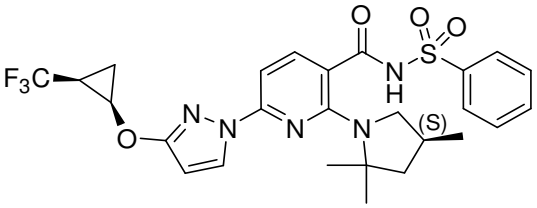

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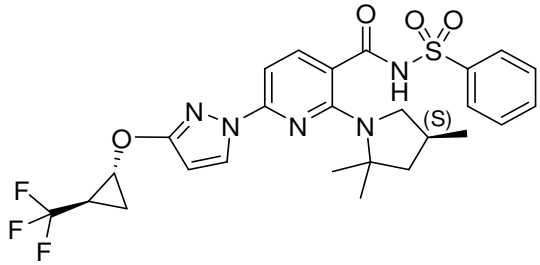

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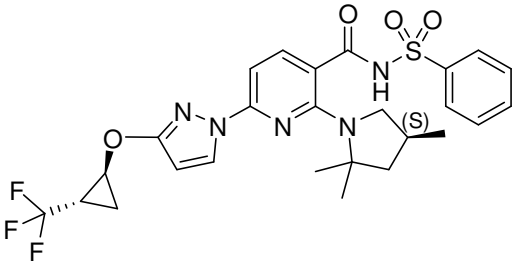

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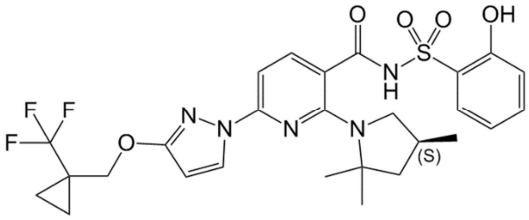

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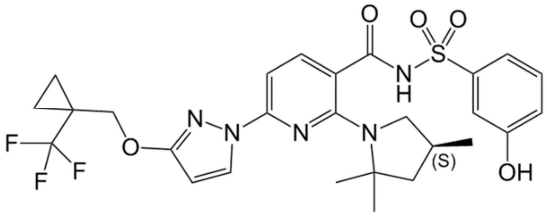

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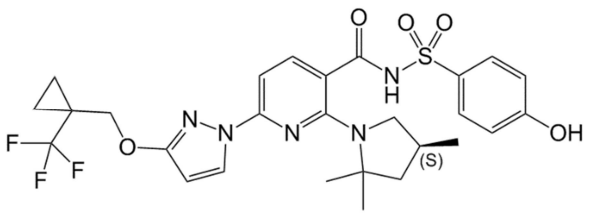

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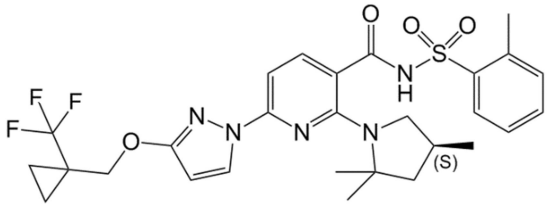

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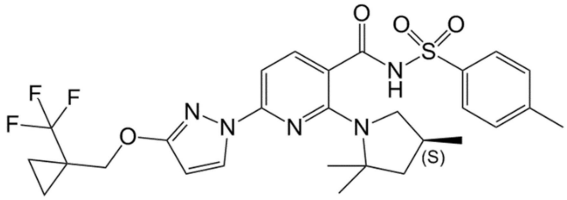

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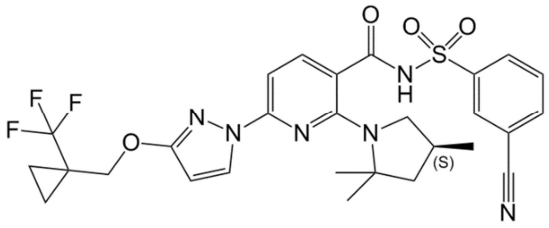

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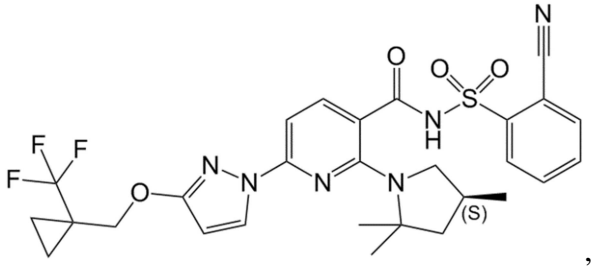

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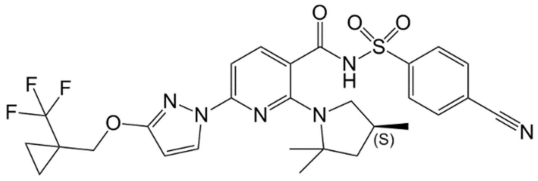

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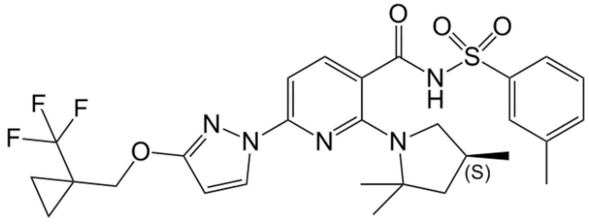

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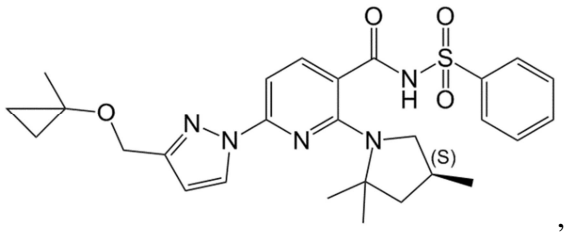
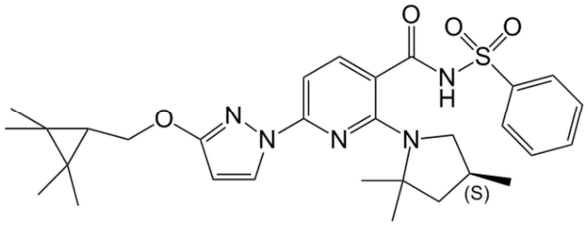
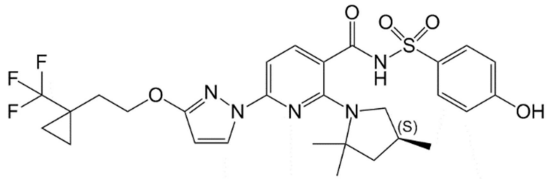
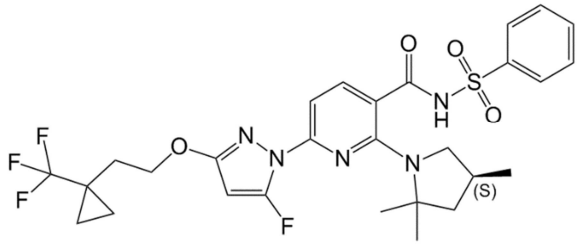
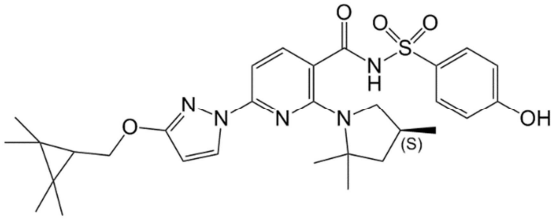
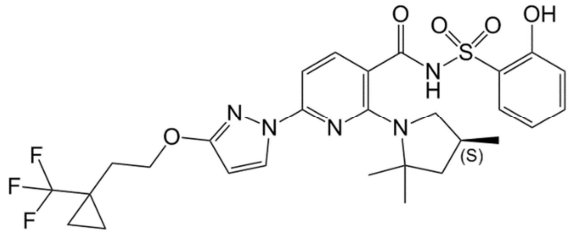
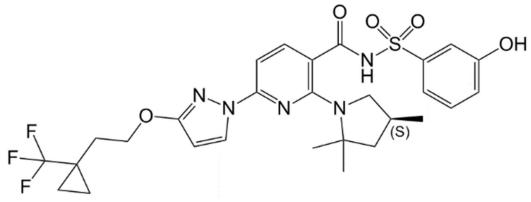

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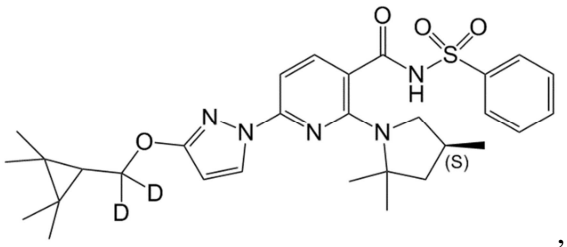

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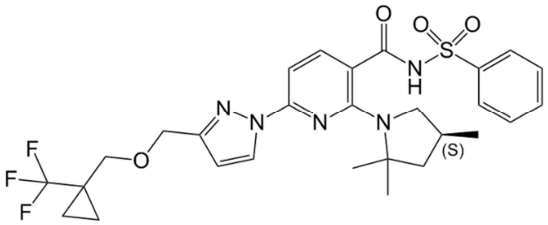

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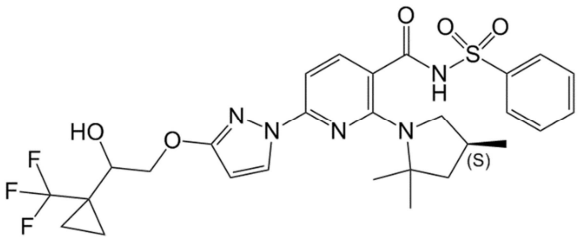

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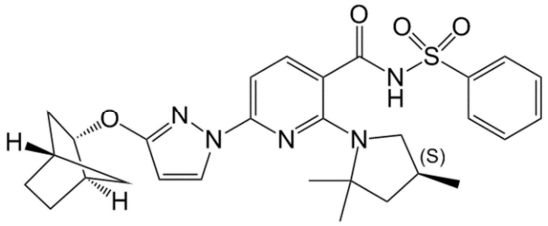

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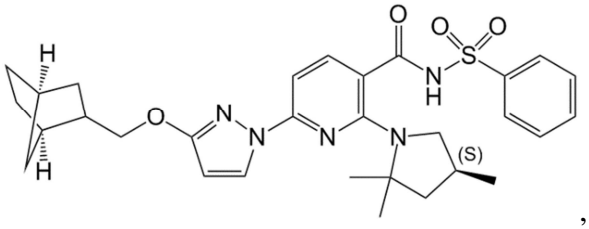

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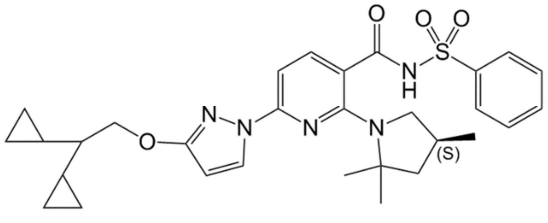

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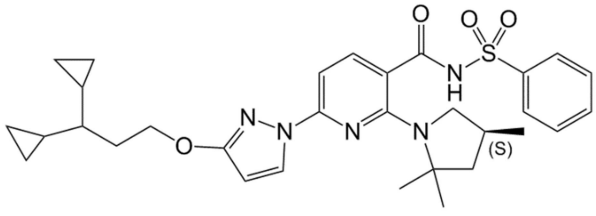

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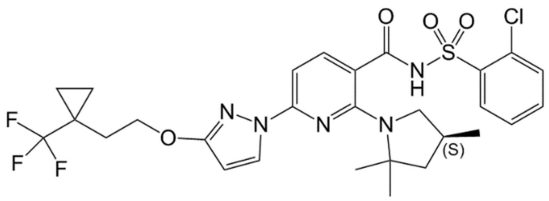

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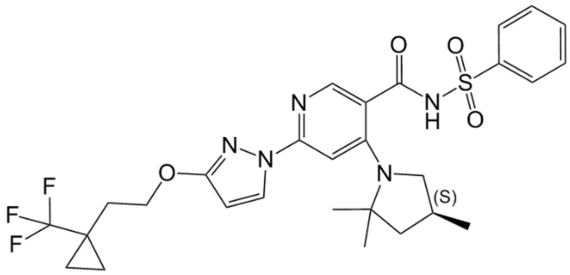

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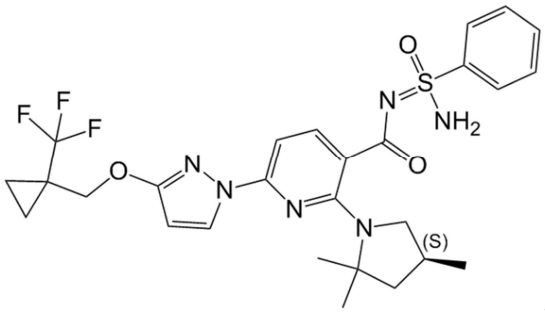

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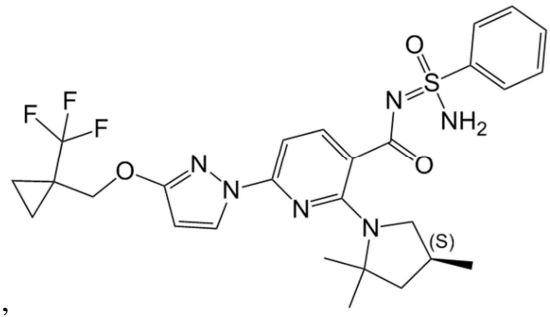

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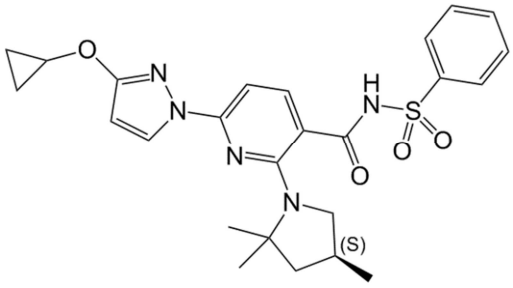

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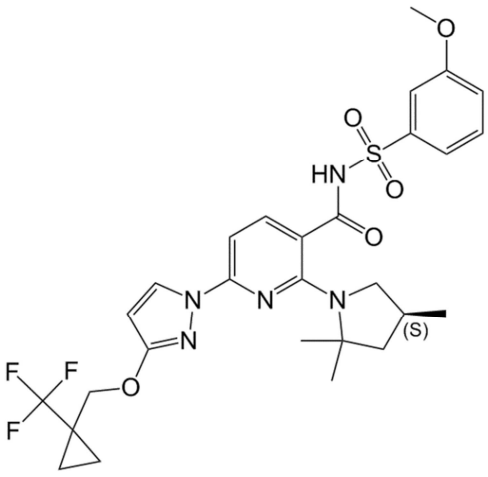

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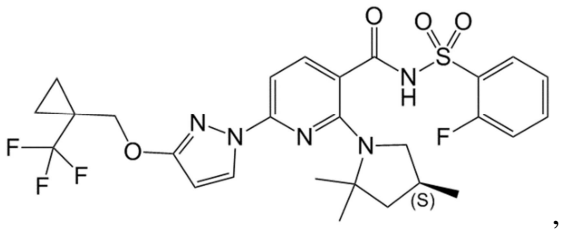

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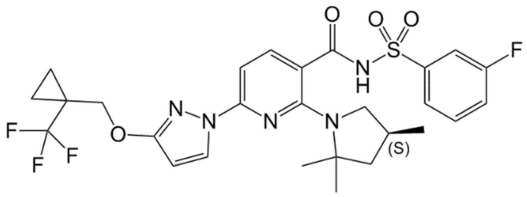

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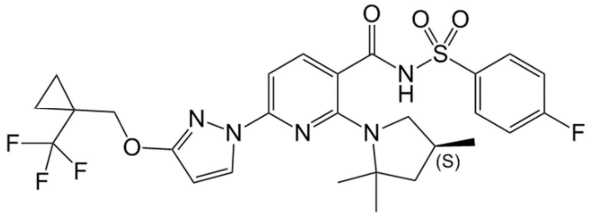
diastereomer 1 diastereomer 2

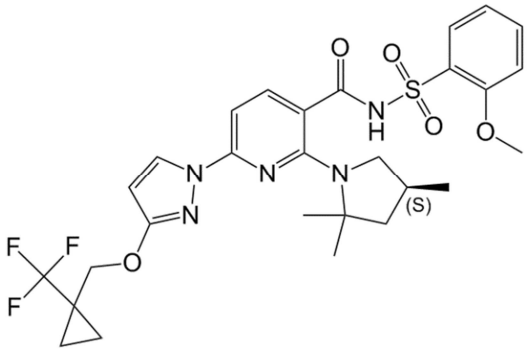

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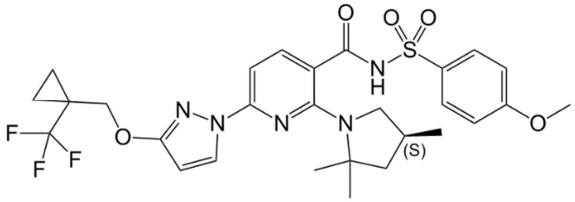

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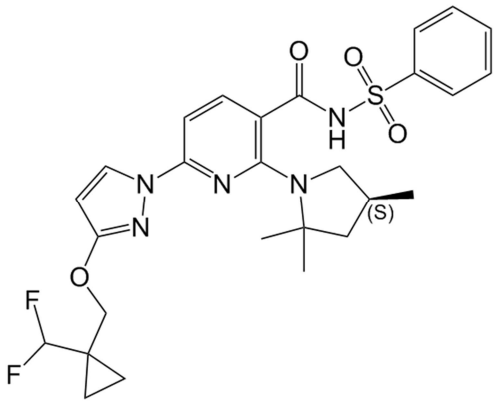

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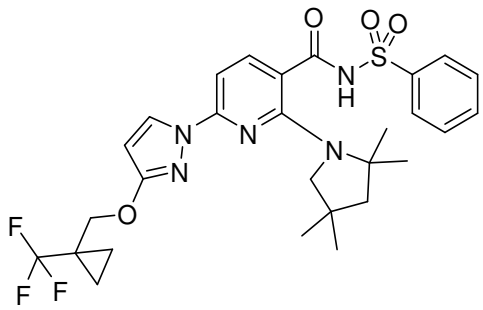

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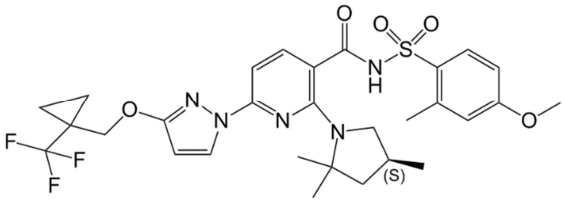

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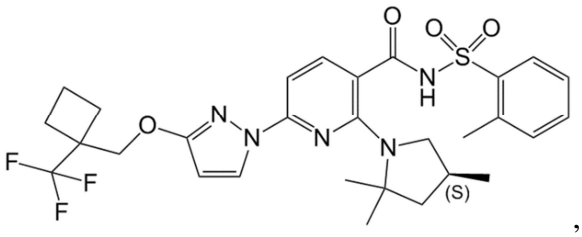

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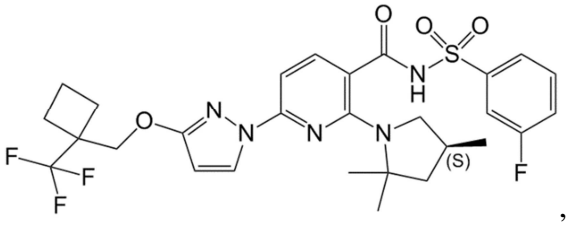

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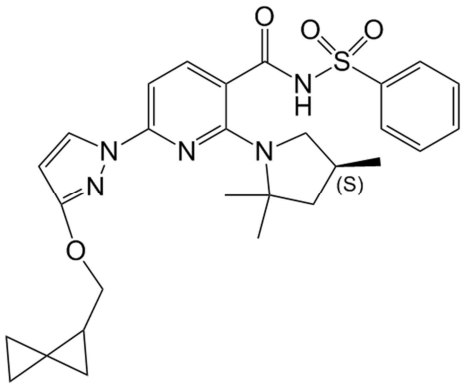

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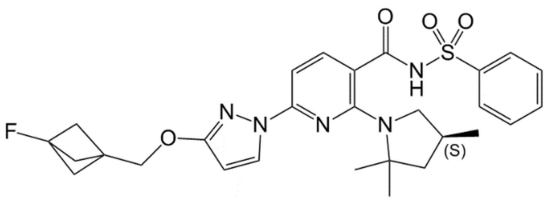

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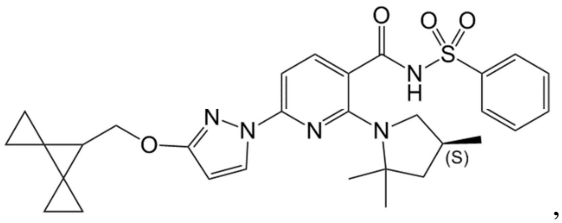

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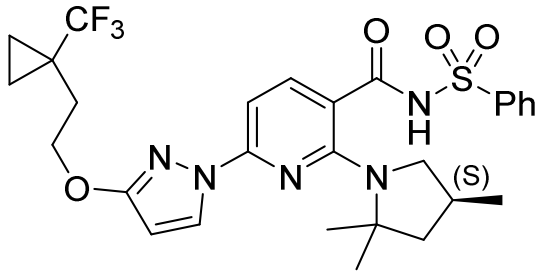

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a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing.

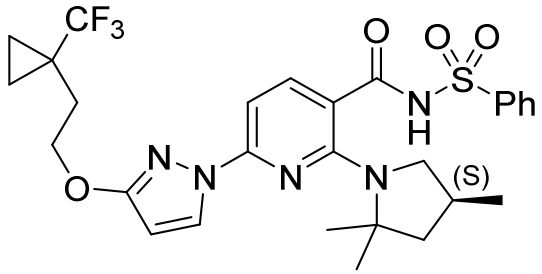
15. A compound according to claim 1 having the following formula:



,

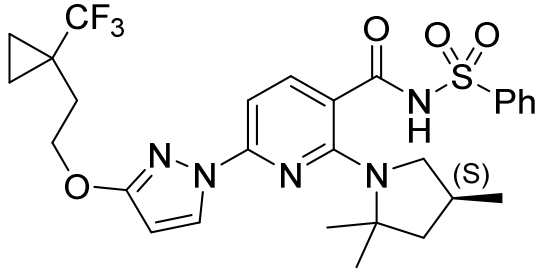
a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing.

16. A compound according to claim 15 having the following formula:



in the form of a pharmaceutically acceptable salt.

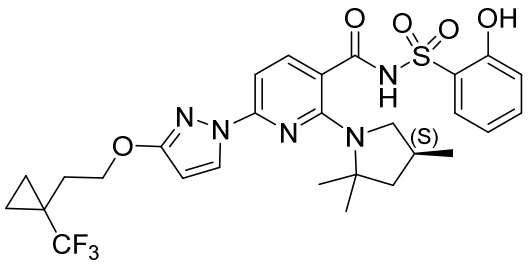
17. A compound according to claim 15 having the following formula:



.

18. A compound according to claim 1 having:

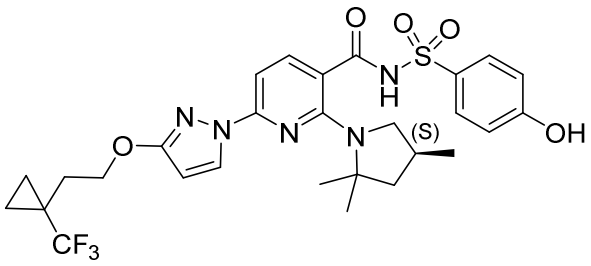
(a) the following formula:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; or

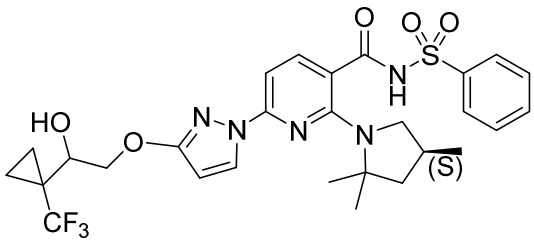
(b) the following formula:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; or

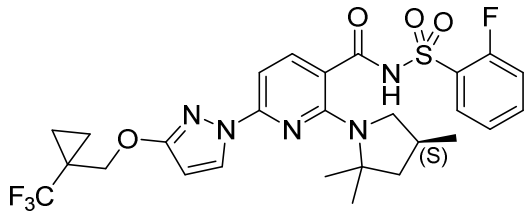
(c) the following formula:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; or

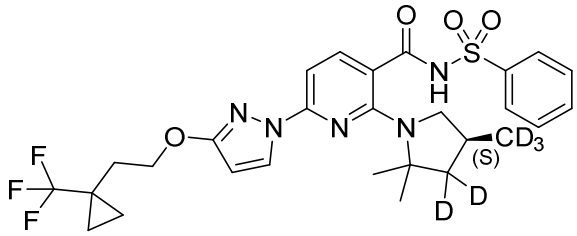
(d) the following formula:



,

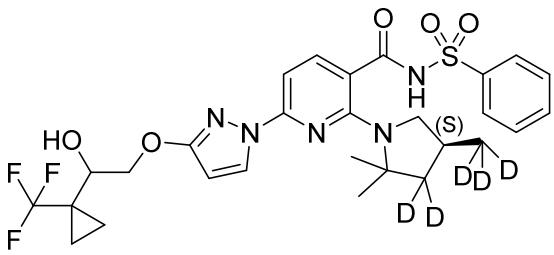
a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; or

(e) the following formula:



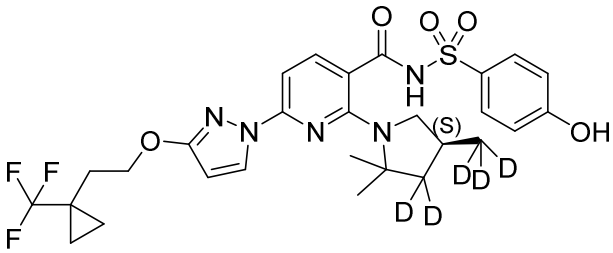
or a pharmaceutically acceptable salt thereof.

(f) the following formula:



or a pharmaceutically acceptable salt thereof; or

(g) the following formula:



or a pharmaceutically acceptable salt thereof.

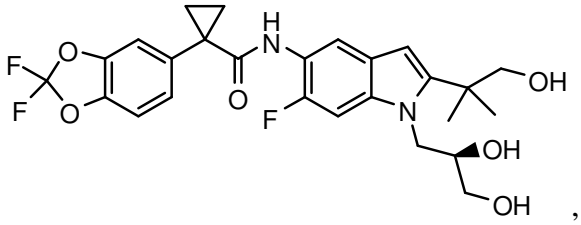
19. A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, as defined in claim 15.

20. A pharmaceutical composition comprising the pharmaceutically acceptable salt of claim 16.

21. A pharmaceutical composition comprising the compound of claim 17.

22. A pharmaceutical composition comprising at least one compound chosen from compounds of any one of claims 1-18, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, and optionally one or more of:

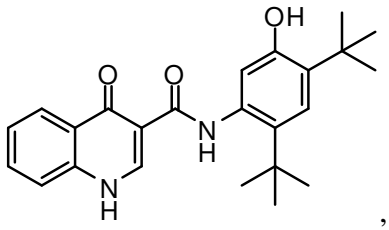
(a) Compound II:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing;

(b) Compound III:



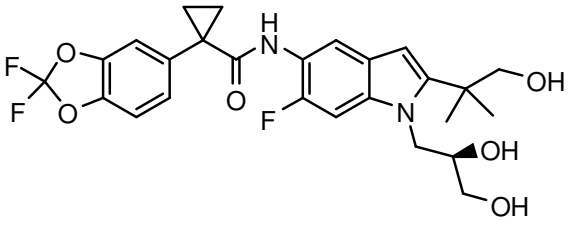
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a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; and

(c) a pharmaceutically acceptable carrier.

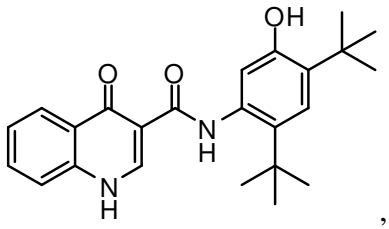
23. The pharmaceutical composition of claim 22 comprising the compound of claim 15 or a pharmaceutically acceptable salt thereof, and optionally one or more of:

(a) Compound II:



or a pharmaceutically acceptable salt thereof;

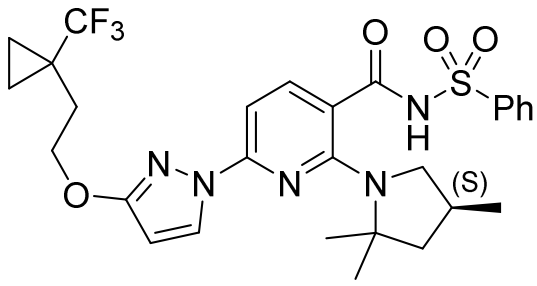
(b) Compound III:



or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, wherein the compound having the formula:



is in the form of a pharmaceutically acceptable salt.

25. The pharmaceutical composition according to claim 22 for use in a method of treating cystic fibrosis

26. The compound, pharmaceutically acceptable salt thereof, or deuterated derivative of any of the foregoing, according to claim 15 for use in a method of treating cystic fibrosis.

27. The pharmaceutically acceptable salt according to claim 16 for use in a method of treating cystic fibrosis.

28. The compound according to claim 17 for use in a method of treating cystic fibrosis.

29. The pharmaceutical composition according to claim 19 for use in a method of treating cystic fibrosis.

30. The pharmaceutical composition according to claim 20 for use in a method of treating cystic fibrosis.

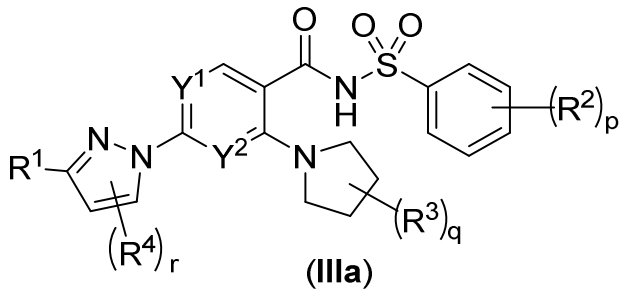
31. The pharmaceutical composition according to claim 21 for use in a method of treating cystic fibrosis.

32. Use of a compound according to any one of claims 1-18 in the manufacture of a medicament for the treatment of cystic fibrosis.

33. The pharmaceutical composition according to claim 23 for use in a method of treating cystic fibrosis.

34. The pharmaceutical composition according to claim 24 for use in a method of treating cystic fibrosis.

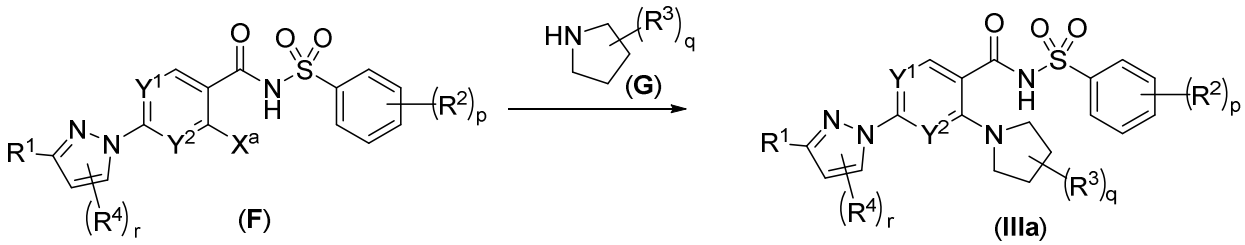
35. A method of preparing a compound of Formula (IIIa):



(IIIa)

,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, comprising reacting a compound of Formula (F) or a salt thereof with a compound of Formula (G) or a salt thereof to generate said compound of Formula (IIIa) or a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing:



wherein in each of said formulae:

- one of Y^1 and Y^2 is N and the other is CH;

- each $\mathbf{R^1}$ is independently chosen from $-(C\mathbf{R}_2)_k$-O-$(C\mathbf{R}_2)_m(C\mathbf{R})_n(\mathbf{Ring\ A})_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each $\mathbf{R^3}$ is independently chosen from C_1-C_2 alkyl groups optionally substituted with one or more OH groups;

- each $\mathbf{R^4}$ is independently chosen from halogens;

- X^a is chosen from F or Cl;

- each k is independently 0 or 1;

- each r is independently 0 or 1;

- each m is independently 0, 1, 2, or 3;

- each n is independently 0 or 1;

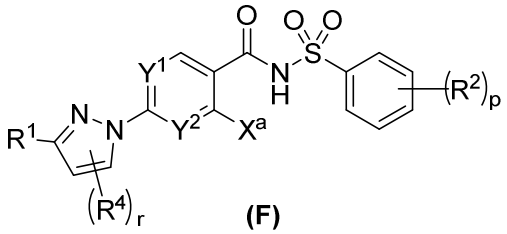
- each p is independently 0, 1, 2, 3, 4, or 5; and

- each q is independently 0, 1, 2, 3, 4, 5, 6, 7, or 8; optionally, wherein each Y^2 is independently N; and each Y^1 is independently CH.

36. The method of claim 35, wherein said reacting a compound of Formula (F) or a salt thereof with a compound of Formula (G) or a salt thereof is performed in the presence of a base.

37. The method of claims 35 or 36, wherein a salt of compound of Formula (G) is employed; optionally, wherein said salt of compound of Formula (G) is a HCl salt of a compound of Formula (G).

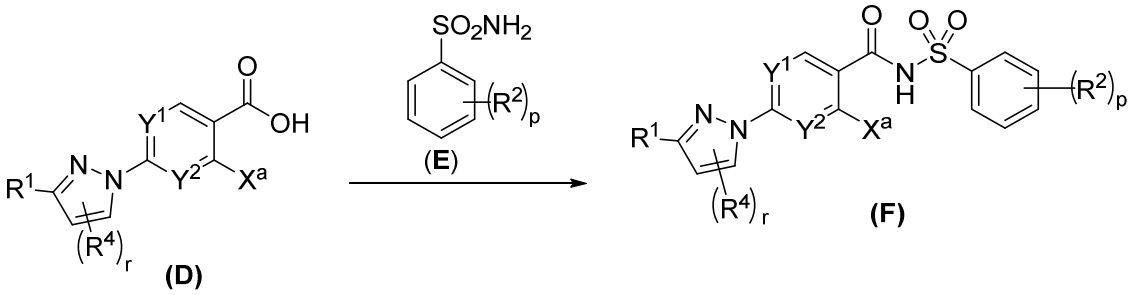
38. A method of preparing a compound of Formula (F) or a salt thereof:



(F)

,

or a deuterated derivative of any of the foregoing, comprising reacting a compound of Formula (D) or salt thereof with a compound of Formula (E) or a salt thereof to generate a compound of Formula (F) or a salt thereof:



(D) **(F)**

,

wherein in each of said formulae:

- one of Y^1 and Y^2 is independently N and the other is independently CH;

- each $\mathbf{R^1}$ is independently chosen from $-(C\mathbf{R}_2)_k\text{-}O\text{-}(C\mathbf{R}_2)_m(C\mathbf{R})_n(\mathbf{Ring\ A})_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each $\mathbf{R^4}$ is independently chosen from halogens;

- X^a is chosen from F or Cl;

- each k is independently 0 or 1;

- each r is independently 0 or 1;

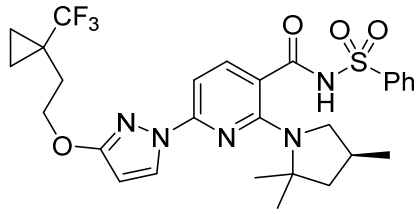
- each m is independently 0, 1, 2, or 3;

- each n is independently 0 or 1; and

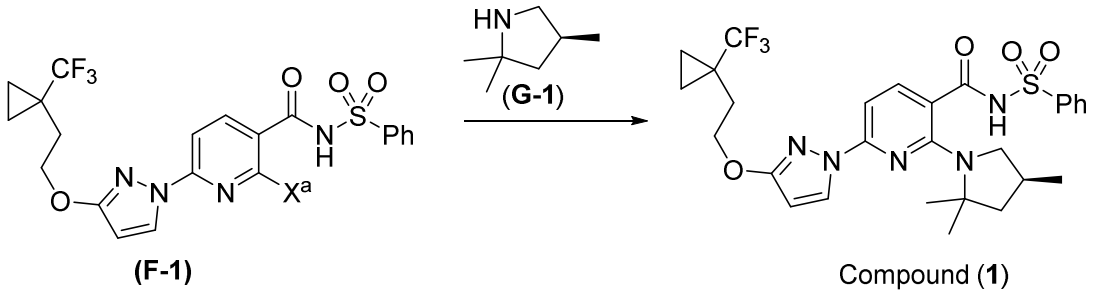
- each p is independently 0, 1, 2, 3, 4, or 5; optionally, wherein each Y^2 is independently N; and each Y^1 is independently CH.

39. The method of claim 38, wherein said reacting a compound of Formula (D) or a salt thereof with a compound of Formula (E) or salt thereof is performed in the presence of a base; or comprises reacting a compound of Formula (D-1) with a coupling reagent and subsequently with a compound of Formula (E-1) in the presence of a base.

40. The method of claim 35 which is a method of preparing a compound of the following formula:



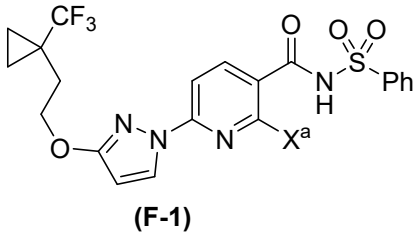
or a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, comprising reacting a compound of Formula (F-1) or a salt thereof, wherein X^a is chosen from F or Cl, with a compound of Formula (G-1) or a salt thereof to generate said compound or a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing:



optionally, wherein said reacting a compound of Formula (F-1) or a salt thereof with a compound of Formula (G-1) or a salt thereof is performed in the presence of a base.

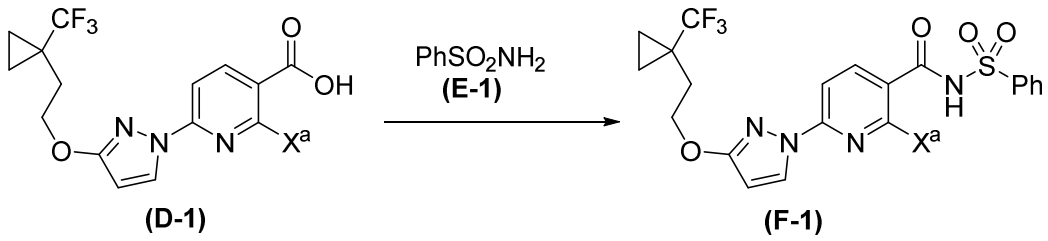
41. The method of claim 40, wherein a salt of compound of Formula (G-1) is employed; optionally, wherein said salt of compound of Formula (G-1) is a HCl salt of a compound of Formula (G-1).

42. The method of claim 38 which is a method of preparing a compound of Formula (F-1) or a salt thereof:



,

or a deuterated derivative of any of the foregoing, comprising reacting a compound of Formula (D-1) and a compound of Formula (E-1) to generate a compound of Formula (F-1) or a salt thereof:

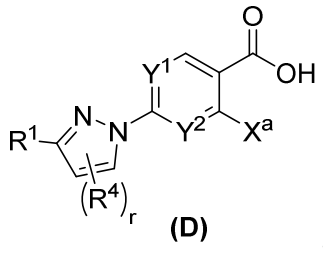


,

wherein each X^a is independently chosen from F or Cl.

43. The method of claim 42, wherein said reacting a compound of Formula (D-1) or a salt thereof with a compound of Formula (E-1) or a salt thereof is performed in the presence of a base; or comprises reacting a compound of Formula (D-1) with a coupling reagent and subsequently with a compound of Formula (E-1) in the presence of a base.

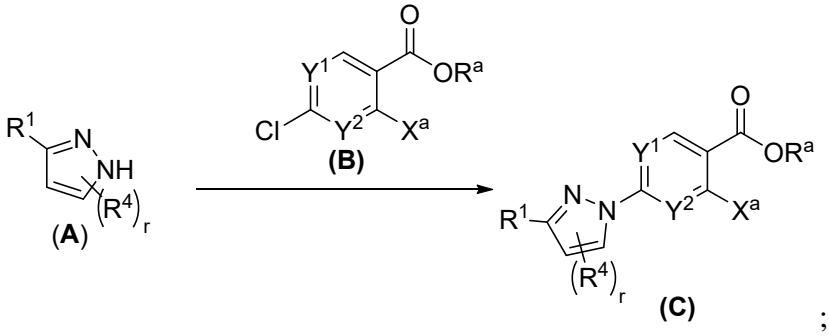
44. A method of preparing a compound of Formula (D) or a salt thereof:



(D) ,

or a deuterated derivative of any of the foregoing, comprising:

(i) reacting a compound of Formula (A) or a salt thereof with a compound of Formula (B) or a salt thereof to generate a compound of Formula (C) or a salt thereof:



; and

(ii) hydrolyzing the $-C(O)OR^a$ group of a compound of Formula (C) to generate a compound of Formula (D) or a salt thereof, wherein in each said formulae:

- one of Y^1 and Y^2 is independently N and the other is independently CH;

- each $\mathbf{R^1}$ is independently chosen from $-(C\mathbf{R}_2)_k\text{-}O\text{-}(C\mathbf{R}_2)_m(C\mathbf{R})_n(\mathbf{Ring\ A})_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^4}$ is independently chosen from halogens;

--each R^a is independently chosen from C_1-C_4 alkyl;

- each X^a is independently chosen from F or Cl;

- each k is independently 0 or 1;

- each r is independently 0 or 1;

- each m is independently 0, 1, 2, or 3; and

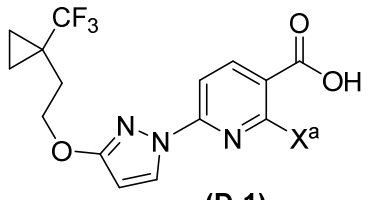
- each n is independently 0 or 1;

optionally, wherein each Y^2 is independently N; and each Y^1 is independently CH.

45. The method of claim 44, wherein the hydrolysis of the –C(O)OR^a group is performed in the presence of a base; optionally, wherein said reacting a compound of Formula (A) or a salt thereof with a compound of Formula (B) or salt thereof is performed in the presence of a base.

46. The method of claim 44 or 45, wherein R^a is ethyl or *t*-butyl.

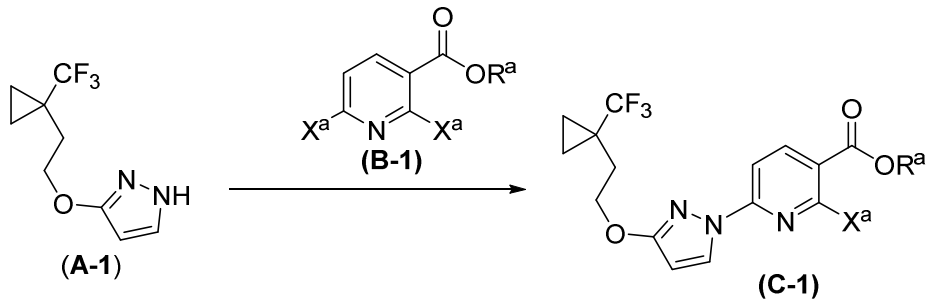
47. The method of claim 44 which is a method of preparing a compound of Formula (D-1) or a salt thereof:



(D-1) ,

or a deuterated derivative of any of the foregoing, comprising:

(i) reacting a compound of Formula (A-1) or a salt thereof and a compound of Formula (B-1) or a salt thereof to generate a compound of Formula (C-1) or a salt thereof:



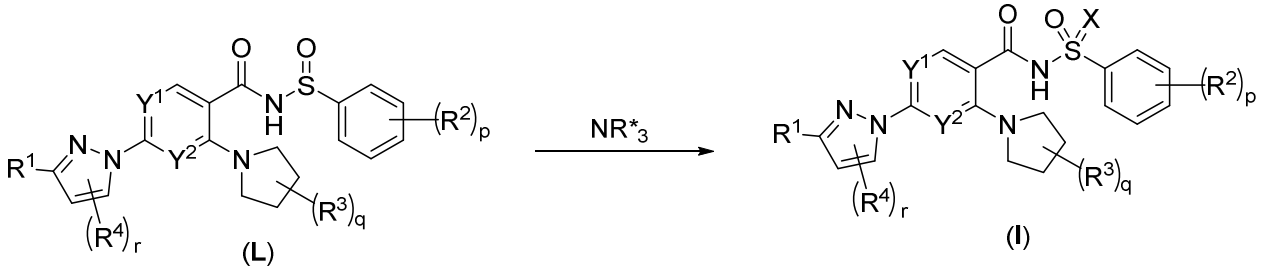
; and

(ii) hydrolyzing the –C(O)OR^a group of a compound of Formula (C-1) or a salt thereof to generate a compound of Formula (D-1) or a salt thereof,

wherein each R^a is independently chosen from C_1-C_4 alkyl; and each - X^a is independently chosen from F or Cl; optionally, wherein the hydrolysis of the –C(O)OR^a group is performed in the presence of a base.

48. The method of claim 47, wherein said reacting a compound of Formula (A-1) or a salt thereof and a compound of Formula (B-1) or a salt thereof is performed in the presence of a base; optionally, wherein R^a is ethyl or *t*-butyl.

49. A method of preparing a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, comprising reacting a compound of Formula (L) or a salt thereof with NR*$_3$:



wherein in each of said formulae:

-- X is NH or N(C_1-C_4 alkyl);

- one of Y^1 and Y^2 is independently N and the other is independently CH;

- each **R^1** is independently chosen from –(C**R**$_2$)$_k$-O-(C**R**$_2$)$_m$(C**R**)$_n$(**Ring A**)$_{n+1}$ groups,

wherein each **Ring A** is independently chosen from C_3-C_{10} cycloalkyl groups optionally substituted with one or more substituents each independently

chosen from C_1-C_2 alkyl groups, halogenated C_1-C_2 alkyl groups, and halogens, and

wherein each **R** is independently chosen from H, OH, and C_1-C_2 alkyl groups optionally substituted with one or more halogens;

- each $\mathbf{R^2}$ is independently chosen from C_1-C_2 alkyl groups, OH, C_1-C_2 alkoxy groups, halogens, and cyano;

- each $\mathbf{R^3}$ is independently chosen from C_1-C_2 alkyl groups optionally substituted with one or more OH groups;

- each $\mathbf{R^4}$ is independently chosen from halogens;

- R* is H or C_1-C_4 alkyl.

- X^a is chosen from F or Cl;

- each k is independently 0 or 1;

- each r is independently 0 or 1;

- each m is independently 0, 1, 2, or 3;

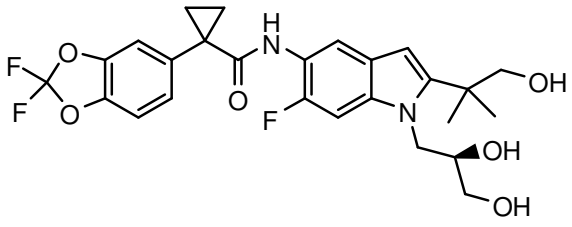
- each n is independently 0 or 1;

- each p is independently 0, 1, 2, 3, 4, or 5; and

- each q is independently 0, 1, 2, 3, 4, 5, 6, 7, or 8.

50. At least one compound chosen from compounds of any one of claims 1-18, a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing, and optionally one or more of:

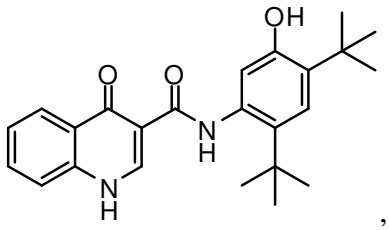
(a) Compound II:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; and

(b) Compound III:



,

a pharmaceutically acceptable salt thereof, or a deuterated derivative of any of the foregoing; for use in treating cystic fibrosis.