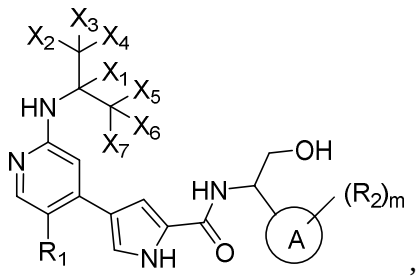
What is claimed is:

1. A compound of Formula 1:



,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein each of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is independently selected from the group consisting of hydrogen, deuterium, and C_{1-4} aliphatic, and wherein:

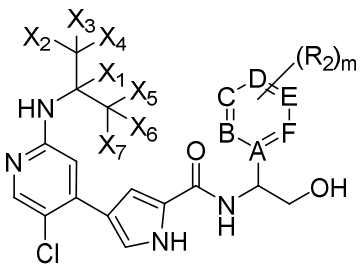
R_1 is hydrogen, C_{1-3} aliphatic, fluoro, or chloro;

A is an optionally substituted group selected from phenyl, a 5-6 membered monocyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, $-NO_2$, $-SO_2R$, -SOR, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $N(R)_2$, wherein each R is independently hydrogen or C_{1-4} aliphatic; and

m is 0, 1, or 2.

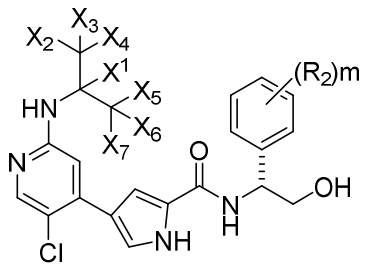
2. A compound of Formula 2A:



2A

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein: each X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are independently selected from hydrogen and deuterium or C_{1-4} aliphatic; R^2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, $-NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $N(R)_2$, wherein each R is independently hydrogen or C_{1-4} aliphatic; m is 0, 1, or 2; and A, B, C, D, E, and F are independently selected from carbon or nitrogen.

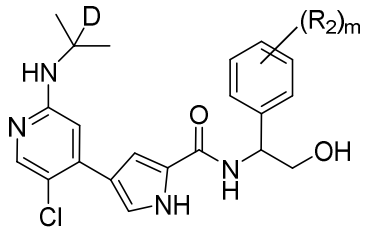
3. A compound of Formula 2B:



2B

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein: each X_1, X_2, X_3, X_4, X_5, X_6, and X_7 are independently selected from hydrogen and deuterium or C_{1-4} aliphatic; R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, $-NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $N(R)_2$, wherein each R is independently hydrogen or C_{1-4} aliphatic; and m is 0, 1, or 2.

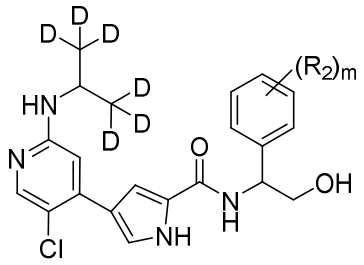
4. A compound of Formula 3A:



3A

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein: R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N(R_2, -NRC(O)R, -NRC(O)N(R_2, -NRSO_2R, or N(R_2, wherein each R is independently hydrogen or C_{1-4} aliphatic; and m is 0, 1, or 2.

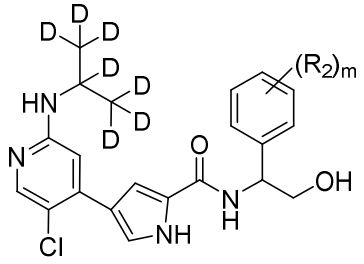
5. A compound of Formula 3B:



3B

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein: R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N(R_2, -NRC(O)R, -NRC(O)N(R_2, -NRSO_2R, or N(R_2, wherein each R is independently hydrogen or C_{1-4} aliphatic; and m is 0, 1, or 2.

6. A compound of Formula 3C:

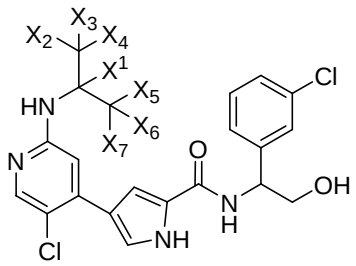


3C

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein: R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N(R_2, -

NRC(O)R, -NRC(O)N(R)$_2$, -NRSO$_2$R, or N(R)$_2$, wherein each R is independently hydrogen or C$_{1-4}$ aliphatic; and m is 0, 1, or 2.

7. A compound of Formula 4:



4

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

each X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is independently selected from hydrogen and deuterium or C$_{1-4}$ aliphatic.

8. The compound of claim 1, which is selected from:

4-(5-chloro-2-((propan-2-yl-d7)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-1,1,1,3,3,3-d6)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-1,1,1,2,3-d5)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-1,1,1,2-d4)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-1,1,2-d3)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-1,2-d2)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

4-(5-chloro-2-((propan-2-yl-2-d1)amino)pyridin-4-yl)-N-(1-(3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide,

and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

9. The compound of any one of claims 1-8, which is an enantiomerically pure 1*S*- or 1*R*-ulixertinib analog.

10. The compound of any one of claims 1-8, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

11. The compound of any one of claims 1-8, wherein each of said positions having deuterium has deuterium enrichment of at least 1%.

12. A pharmaceutical composition comprising a compound according to any one of claims 1-8 and a pharmaceutically acceptable carrier, excipient or vehicle.

13. Use of a compound according to any one of claims 1-8 or the pharmaceutical composition of claim 12 in the manufacture of a medicament for the treatment of a disease, disorder, or condition in a subject in need thereof, wherein the disease, disorder, or condition comprises one or more of cancer, autoimmune disorders, neurodegenerative and neurological disorders, schizophrenia, bone-related disorders, liver disease, and cardiac disorders.

14. The use of claim 13, wherein after a therapeutically effective amount of the compound or pharmaceutical composition is to be administered, there is a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed cytochrome P_{450} isoform as compared to the corresponding non-isotopically enriched compound.

15. The use of claim 14, wherein the cytochrome P_{450} isoform is selected from the group consisting of CYP3A4, CYP3A5, CYP2C8, CYP2C9, CYP2D6, CYP2C19, CYP1A2, CYP2B6, and CYP2E1.

16. The use of claim 13, wherein the compound decreases inhibition of at least one cytochrome P_{450} per dosage unit thereof as compared to the non-isotopically enriched compound.

17. The use of claim 16, wherein said cytochrome P_{450} is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3ASP1, CYPa5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

18. The compound of claim 1 or pharmaceutical composition of claim 12 for use as a medicament.

19. Use of the compound of claim 1 or pharmaceutical composition of claim 12 in the manufacture of a medicament for the prevention or treatment of a disorder ameliorated by the inhibition of ERK protein kinase.

20. The compound of claims 1 to 8 or pharmaceutical composition of claim 12, wherein each position having deuterium has at least 1% incorporation of deuterium.

21. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least one of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

22. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least two of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

23. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least three of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

24. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least four of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

25. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least five of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

26. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein at least six of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

27. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein each of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium.

28. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein each of X_2, X_3, X_4, X_5, X_6, and X_7 is deuterium, and X^1 is hydrogen.

29. The compound of claim 1 to 3 or pharmaceutical composition of claim 12, wherein each of X_2, X_3, X_4, X_5, X_6, and X_7 is hydrogen, and X^1 is deuterium.

30. An *in vitro* method of inhibiting ERK1/2 in a cell comprising the step of contacting the cell with the compound of claim 1 to 8 or pharmaceutical composition of claim 12.

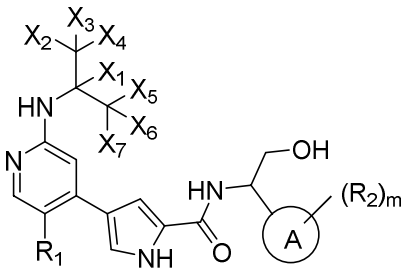
31. The compound of claim 1 to 8 or pharmaceutical composition of claim 12, wherein the compound or pharmaceutical composition is effective to decrease metabolism of the compound or pharmaceutical composition by at least one polymorphically-expressed cytochrome P_{450} isoform as compared to the corresponding non-isotopically enriched compound.

32. The compound or pharmaceutical composition of claim 31, wherein the cytochrome P_{450} isoform is selected from the group consisting of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3ASP1, CYPa5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

33. The compound or pharmaceutical composition of claim 32, wherein the cytochrome P_{450} isoform is selected from the group consisting of CYP3A4, CYP3A5, CYP2C8, CYP2C9, CYP2D6, CYP2C19, CYP1A2, CYP2B6, and CYP2E1.

34. The use of claim 13, wherein after a therapeutically effective amount of the compound or pharmaceutical composition is to be administered to the subject in need thereof, there is a decrease in metabolism of the compound or pharmaceutical composition compared to the corresponding non-deuterated form of the compound or pharmaceutical composition which is at least greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 55%, or greater than about 60% as compared to non-isotopically enriched compound.

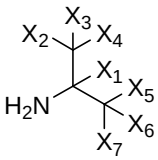
35. A method of synthesizing a deuterated compound according to Formula 1:



Formula 1;

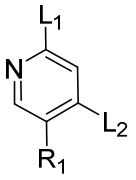
comprising the steps of:

(i) reacting a compound of Formula 5:



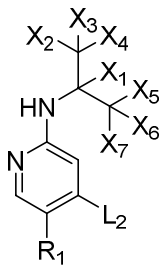
Formula 5;

with a compound of Formula 6:



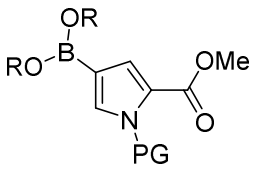
Formula 6;

to produce the compound of Formula 7:



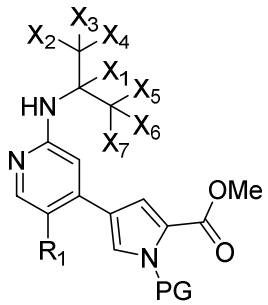
Formula 7;

(ii) reacting the compound of Formula 7 with the compound of Formula 8:



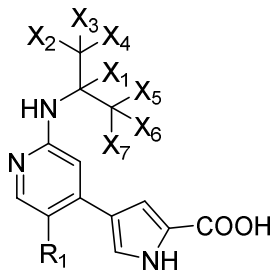
Formula 8;

to produce the compound of Formula 9:



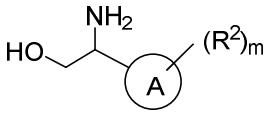
Formula 9;

(iii) reacting the compound of Formula 9 with LiOH to produce the compound of Formula 10:



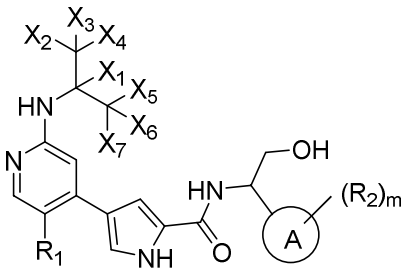
Formula 10;

(iv) reacting the compound of Formula 10 with the compound of Formula 11:



Formula 11;

to produce the compound of Formula 1:



Formula 1.

wherein each of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is independently selected from the group consisting of hydrogen, deuterium, and C_{1-4} aliphatic, and wherein:

R_1 is hydrogen, C_{1-3} aliphatic, fluoro, or chloro;

A is an optionally substituted group selected from phenyl, a 5-6 membered monocyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

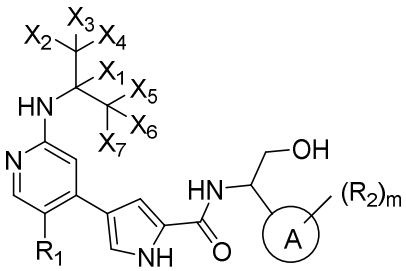
R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N($R)_2$, -NRC(O)R, -NRC(O)N($R)_2$, -NRSO_2R, or N($R)_2$; wherein each R is independently hydrogen or C_{1-4} aliphatic;

m is 0, 1, or 2,

PG is a protecting group; and

L_1 and L_2 are independently selected leaving groups.

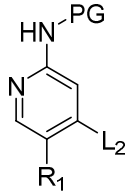
36. A method of synthesizing a deuterated compound according to Formula 1:



Formula 1;

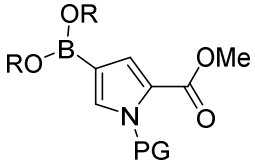
comprising the steps of:

(i) reacting a compound of Formula 12:



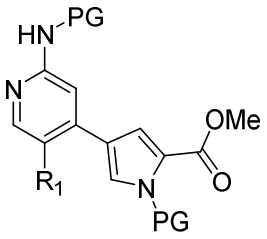
Formula 12;

with a compound of Formula 8:



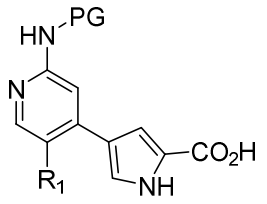
Formula 8;

to produce a compound of Formula 13:

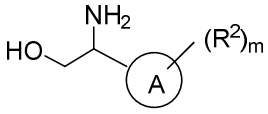


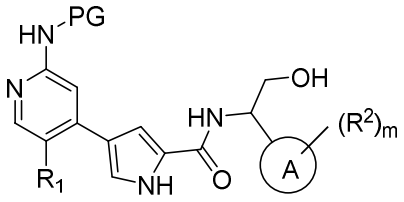
Formula 13;

(ii) reacting the compound of Formula 13 with LiOH to produce the compound of Formula 14:



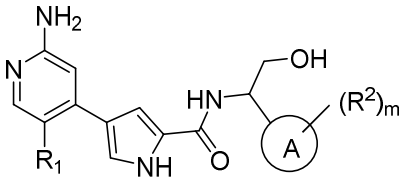
Formula 14;

(iii) reacting the compound of Formula 14 with  to produce the compound of Formula 15:



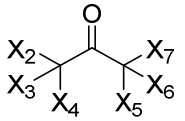
Formula 15;

(iv) deprotecting the compound of Formula 15 to produce the compound of Formula 16:



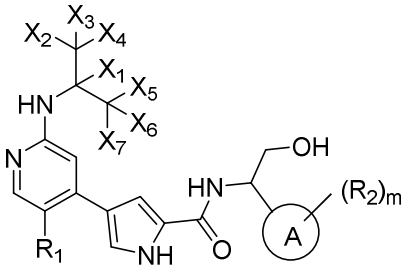
Formula 16;

(v) reacting the compound of Formula 16 with the compound of Formula 17:



Formula 17;

to produce the compound of Formula 1:



Formula 1;

wherein each of X_1, X_2, X_3, X_4, X_5, X_6, and X_7 is independently selected from the group consisting of hydrogen, deuterium, and C_{1-4} aliphatic, and wherein:

R_1 is hydrogen, C_{1-3} aliphatic, fluoro, or chloro;

A is an optionally substituted group selected from phenyl, a 5-6 membered monocyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

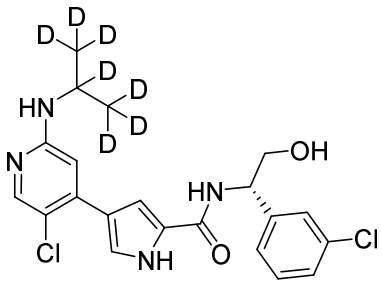
R_2 is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, $-NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $N(R)_2$; wherein each R is independently selected from hydrogen or C1’4 aliphatic;

m is 0, 1, or 2,

PG is a protecting group; and

L_2 is a leaving group.

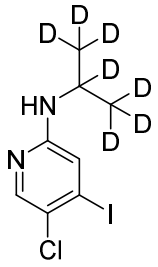
37. A method of synthesizing a deuterated ulixertinib of Formula 18:



Formula 18;

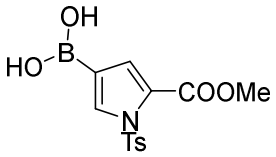
or a pharmaceutically acceptable salt thereof, comprising the steps of:

(i) reacting a compound of Formula 7A:



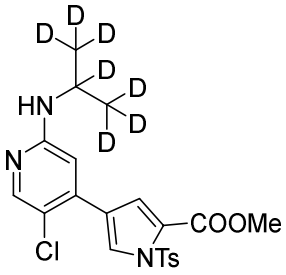
Formula 7A;

with a compound of Formula 8A:



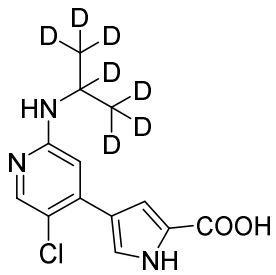
Formula 8A;

to provide the compound of Formula 9A:



Formula 9A;

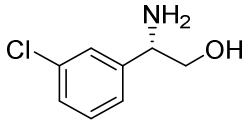
(ii) reacting the compound of Formula 9A with LiOH to produce the compound of Formula 10A:



Formula 10A;

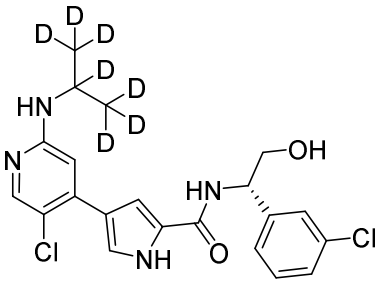
and

(iii) reacting the compound of Formula 10A with the compound of Formula 8B:



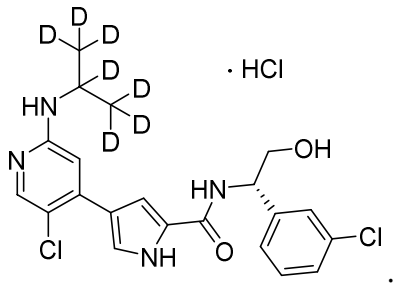
Formula 111888;

to produce the compound of Formula 18:



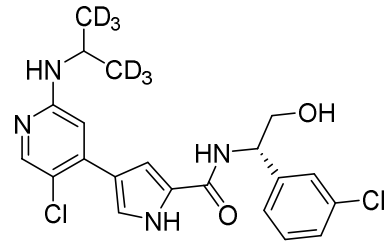
Formula 18.

38. The method of claim 31 further comprising the step of reacting Formula 18 with HCl to produce the compound of Formula 18A:



Formula 18A

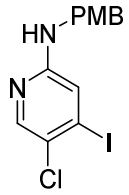
39. A method of synthesizing a deuterated ulixertinib of Formula 19, or a pharmaceutically acceptable salt thereof:



Formula 19;

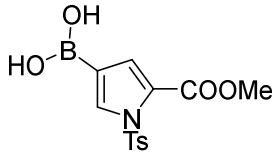
comprising the steps of:

(i) reacting a compound of Formula 12A:



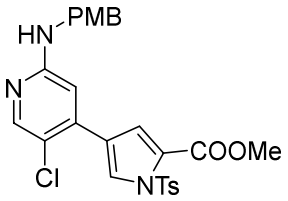
Formula 12A;

with a compound of Formula 8A:



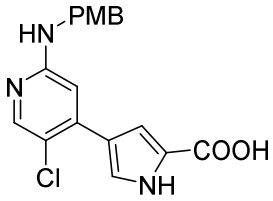
Formula 8A;

to produce a compound of Formula 13A:



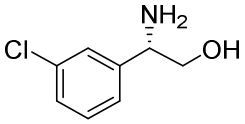
Formula 13A;

(ii) reacting the compound of Formula 13A with LiOH to produce the compound of Formula 14A:



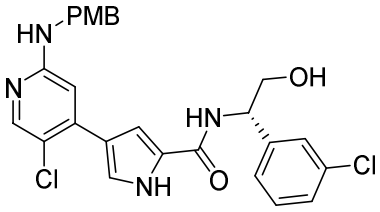
Formula 14A;

(iii) reacting the compound of Formula 14A with the compound of Formula 8B:



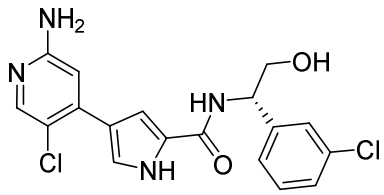
Formula 8B;

to produce a compound of Formula 15A:



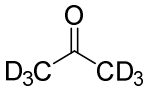
Formula 15A;

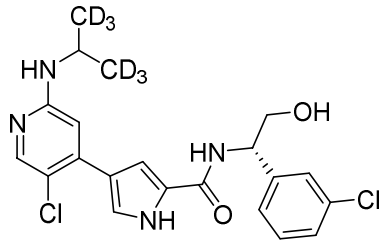
(iv) reacting the compound of Formula 15A with TFA to produce the compound of Formula 16A:



Formula 16A;

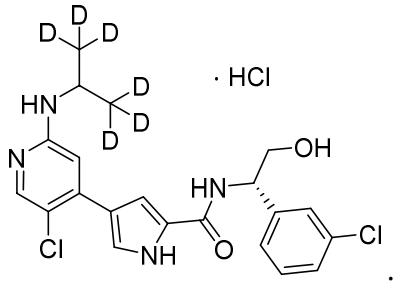
and

(v) reacting the compound of Formula 16A with  to produce the compound of Formula 19:



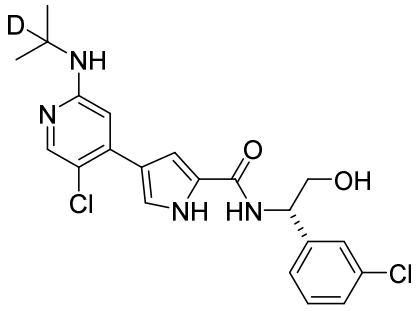
Formula 19.

40. The method of claim 39, further comprising the step of reacting Formula 19 with HCl to produce a compound of formula 19A



19A

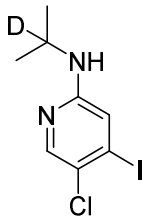
41. A method of synthesizing a deuterated ulixertinib of Formula 21, or a pharmaceutically acceptable salt thereof:



Formula 21;

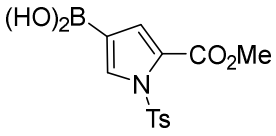
comprising the steps of:

(i) reacting a compound of Formula 7B:



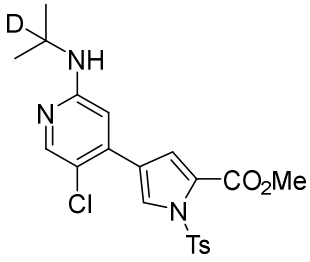
Formula 7B;

with a compound of Formula 8A:



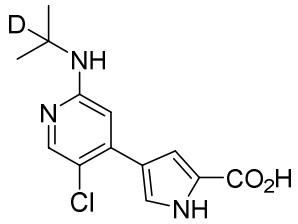
Formula 8A;

to produce a compound of Formula 9B:



Formula 9B;

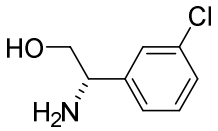
(ii) reacting the compound of Formula 9B with LiOH to produce a compound of Formula 10B:



Formula 10B;

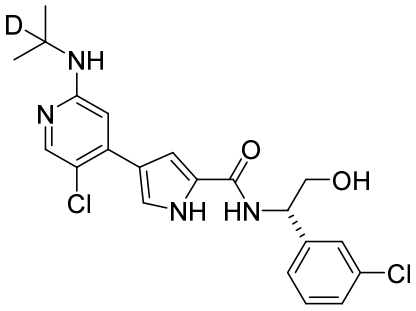
and

(iii) reacting the compound of Formula 10B with the compound of Formula 8B:



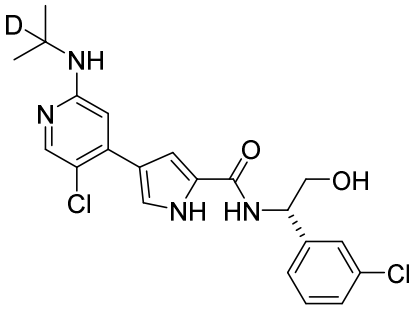
Formula 8B;

to produce the compound of Formula 21:



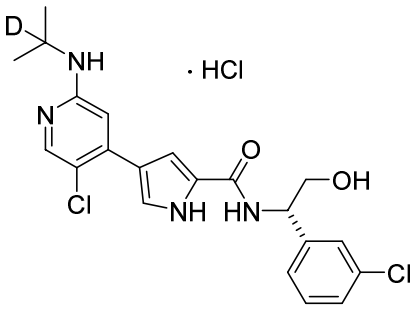
Formula 21.

42. A method of synthesizing a deuterated ulixertinib of Formula 21A comprising the step of reacting a compound of Formula 21:



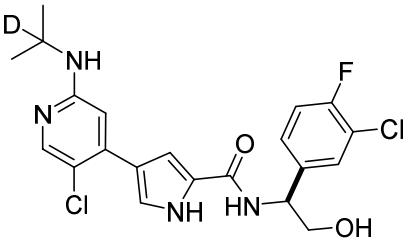
Formula 21

with HCl to produce the compound of Formula 21A:

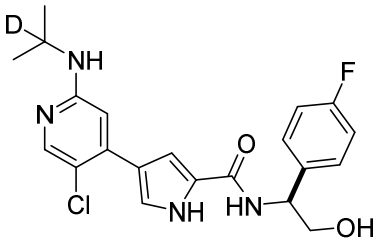


Formula 21A.

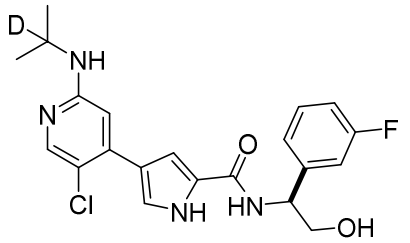
43. A compound selected from:



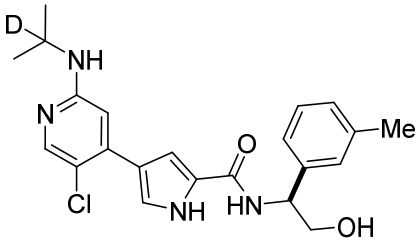
Formula 3A-1



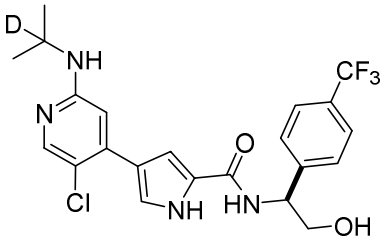
Formula 3A-2



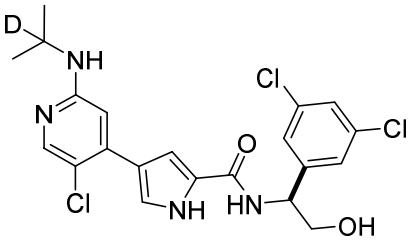
Formula 3A-3



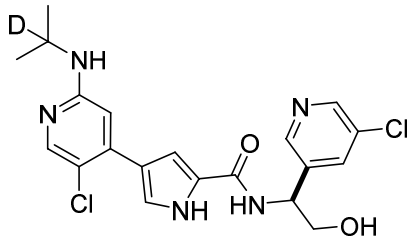
Formula 3A-4



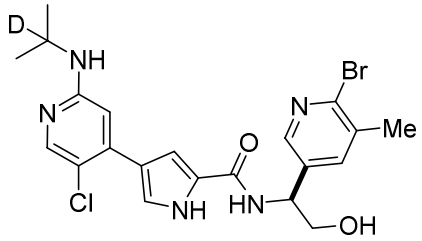
Formula 3A-5



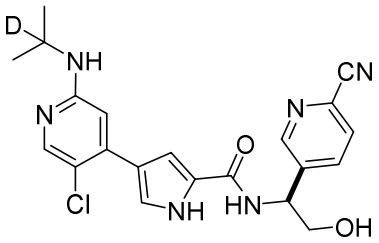
Formula 3A-6



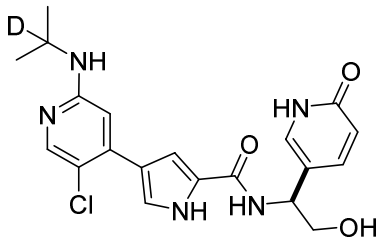
Formula 3A-7



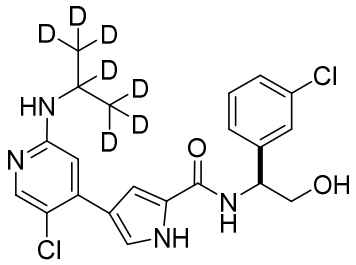
Formula 3A-8



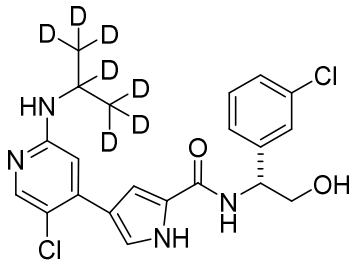
Formula 3A-9



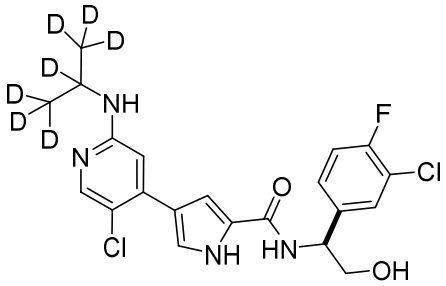
Formula 3A-10



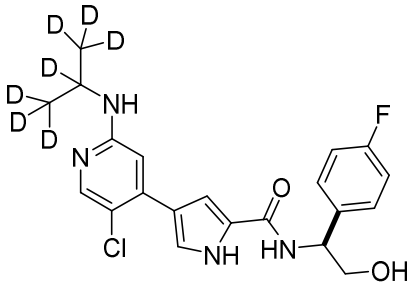
Formula 3C-1



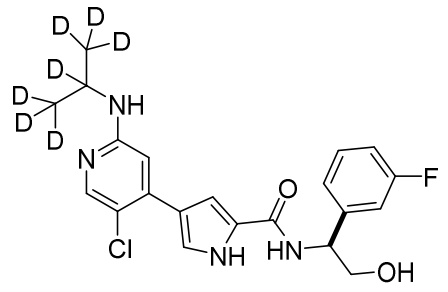
Formula 3C-2



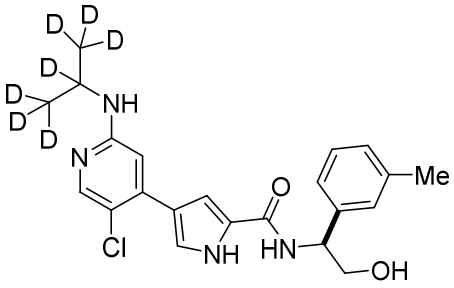
Formula 3C-3



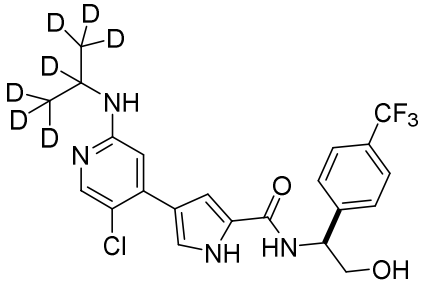
Formula 3C-4



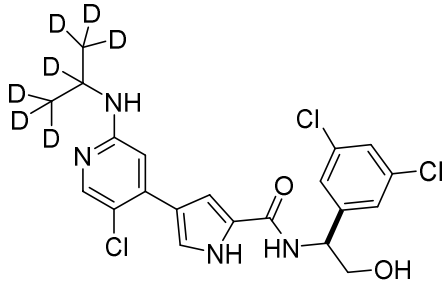
Formula 3C-5



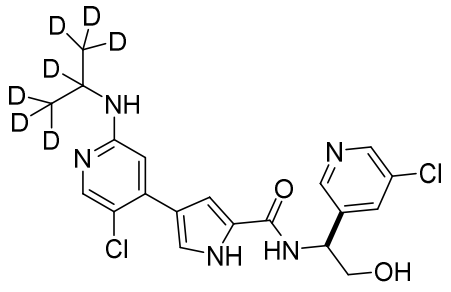
Formula 3C-6



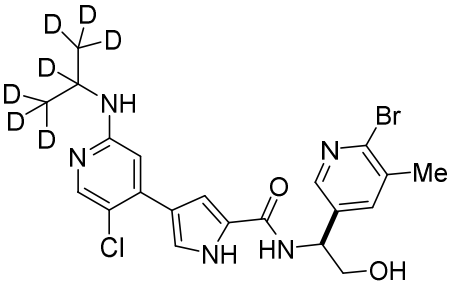
Formula 3C-7



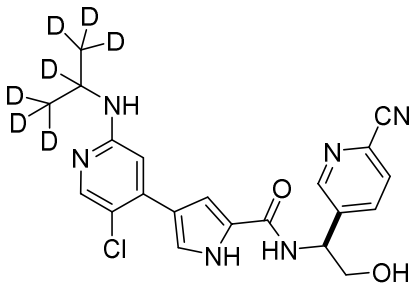
Formula 3C-8



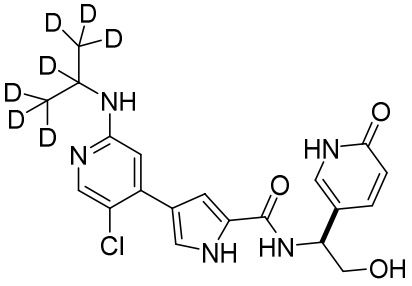
Formula 3C-9



Formula 3C-10



Formula 3C-11



Formula 3C-12

and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

44. A kit for treating or ameliorating the effects of a disease in a subject, the kit comprising a compound according to claims 1-8 or a pharmaceutical composition according to claim 12 packaged together with instructions for its use.

45. The kit according to claim 44, wherein the compound or pharmaceutical composition is effective to decrease metabolism of the compound or pharmaceutical composition by at least one polymorphically-expressed cytochrome P_{450} isoform as compared to the corresponding non-isotopically enriched compound.