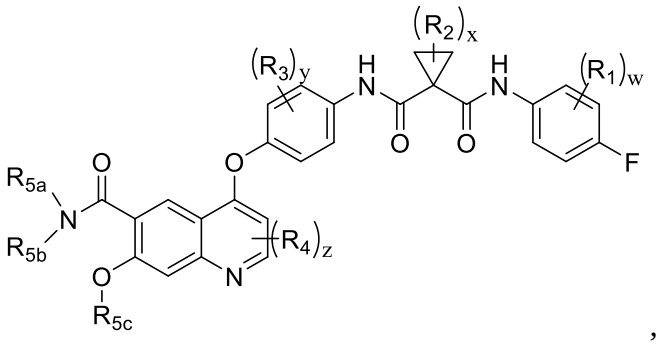
[0005] Therefore, a need exists for compounds, and processes of producing the compounds in high yield and purity, that inhibit TAM receptor tyrosine kinases such as Axl and Mer for the treatment of selected cancers.

SUMMARY

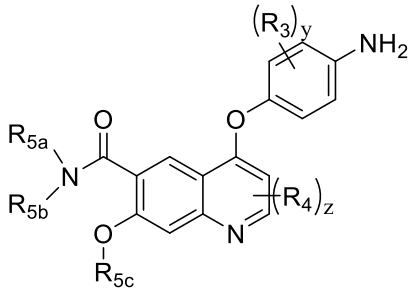
[0005a] In a first aspect of the present disclosure, there is provided a process for preparing a compound of Formula I



,

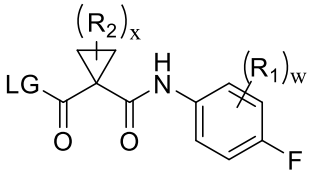
Formula I

or a pharmaceutically acceptable salt thereof, comprising contacting a compound of Formula II



Formula II

with a compound of Formula III



Formula III

in the presence of a solvent and a base, wherein

LG is a leaving group selected from Cl, Br, I, HOAt, HOBt, and an organotriphosphate compound;

R_1 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl;

R_2 and R_3 are each independently selected from halo and C_{1-6} alkyl;

R_4 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl;

R_{5a} is selected from H, OH, NH_2, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl, wherein the up to three methylene units of the C_{1-8} alkyl are optionally and independently replaced with –O-, NR'-, -C(O)-, -C(O)O-, and -C(O)NR'-, wherein R_{5a} is optionally substituted with up to three substituents selected from halo, CN, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', $C(O)NR'_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, and C_{3-6} heteroaryl;

R_{5b} is H or C_{1-6} alkyl; or

R_{5a} and R_{5b} together with the nitrogen to which they are attached form a C_{3-6} heterocycloalkyl optionally substituted with halo, CN, OH, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', $C(O)NR'_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, or C_{3-6} heteroaryl;

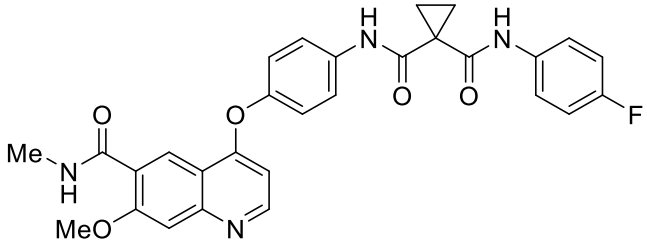
R_{5c} is H or C_{1-6} alkyl optionally substituted with halo, CN, OH, NH_2, or OR';

R' is H or C_{1-6} alkyl, and

w, x, y, and z are each independently an integer from 0 to 4;

and wherein the process optionally further comprises contacting the compound of Formula I with an acid to produce a pharmaceutically acceptable salt of the compound of Formula I.

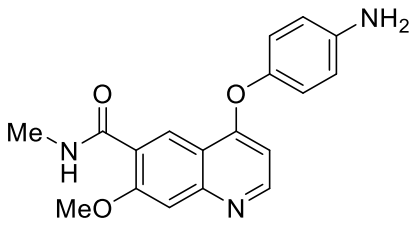
[0005b] In another aspect of the present disclosure, there is provided a process for preparing Compound 1



,

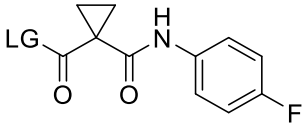
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4



4

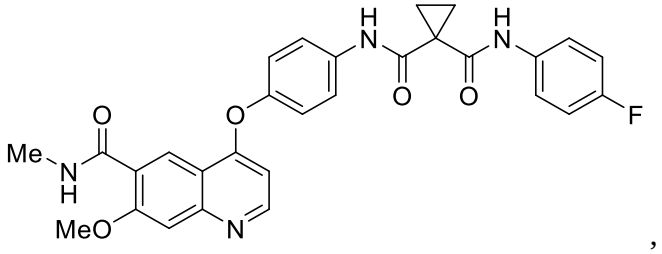
with a compound of Formula III'



Formula III'

in the presence of a solvent and a base, wherein LG is a leaving group selected from Cl, Br, I, HOAt, HOBt, and an organotriphosphate compound, and wherein the process optionally further comprises contacting the compound of Compound 1 with an acid to produce a pharmaceutically acceptable salt of the compound of Compound 1.

[0005c] In yet another aspect of the present disclosure, there is provided a process for preparing Compound 1

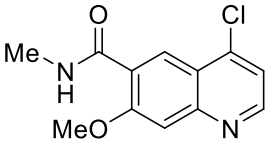


,

1

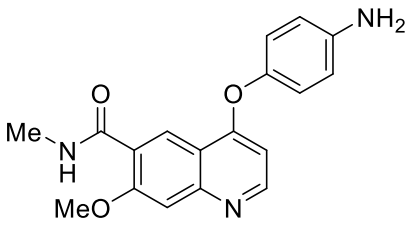
or a pharmaceutically acceptable salt thereof, comprising:

reacting Compound 3



3

with 4-aminophenol (5) in the presence of dimethylacetamide and sodium *t*-pentoxide, at a temperature that is from 75 to 80 ºC, to provide a first reaction mixture comprising Compound 4

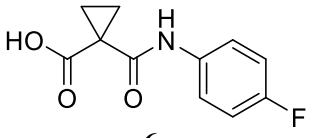


4

;

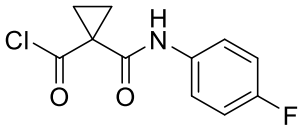
precipitating and isolating Compound 4 as a solid by adding water to the first reaction mixture;

reacting Compound 6



6

with oxalyl chloride in the presence of tetrahydrofuran and a catalytic amount of dimethylformamide at a temperature that is from 5 to 15 ºC to produce a second reaction mixture comprising Compound 7



7

;

adding the second reaction mixture to a third reaction mixture comprising a solvent that is approximately 2:1 tetrahydrofuran:water, a base that is K_2CO_3, and Compound 4, over a period of at least 30 minutes to create a fourth reaction mixture wherein the temperature of the fourth reaction mixture is maintained below approximately 27 ºC during the addition;

heating the fourth reaction mixture to to 35-40 °C and letting stand to separate to an organic phase and an aqueous phase;

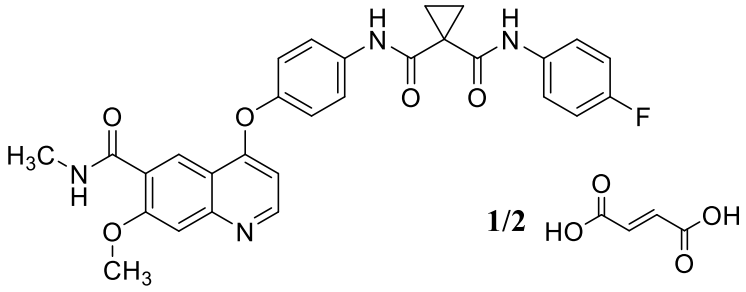
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

adding water to the organic phase over a period of at least one hour to create a fifth reaction mixture;

stirring the fifth reaction mixture for at least 2 hours; and

isolating Compound 1 as a solid product, and wherein the process optionally further comprises contacting the compound of Compound 1 with an acid to produce a pharmaceutically acceptable salt of the compound of Compound 1.

[0005d] In a further aspect of the present disclosure, there is provided a process for preparing Compound 1-hemifumarate



Compound 1-hemifumarate

comprising:

adding a mixture of fumaric acid dissolved in a solvent of 20% solution of water in ethanol at 45-50 ºC to Compound 1 to create a reaction mixture;

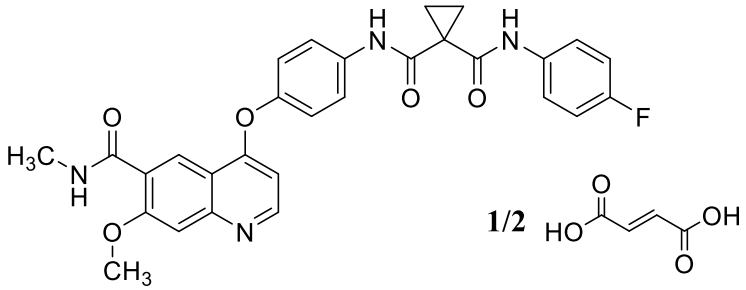
heating the reaction mixture to reflux;

stirring the reaction mixture at reflux for 4-6 hours;

cooling the reaction mixture; and

filtering the reaction mixture to obtain Compound 1·hemifumarate as a solid.

[0005e] In another aspect of the present disclosure, there is provided a process for preparing Compound 1-hemifumarate



Compound 1-hemifumarate

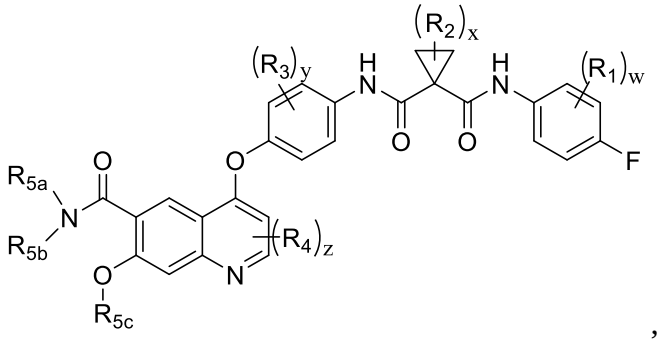
comprising:

combining a fumaric acid solution with Compound 1 to generate a reaction mixture comprising a slurry;

heating the reaction mixture to reflux for a predetermined amount of time; and

isolating Compound 1·hemifumarate as a solid.

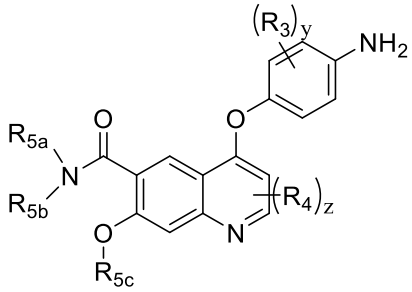
[0006] In one example, the present disclosure includes a process for the preparation of a compound of Formula I



,

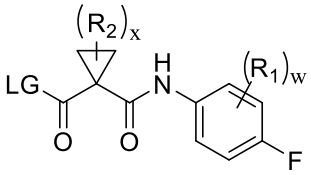
Formula I

or a pharmaceutically acceptable salt thereof, comprising contacting a compound of Formula II



Formula II

with a compound of Formula III



Formula III

in the presence of a solvent and a base, wherein

LG is a leaving group selected from Cl, Br, I, HOAt, HOBt, and an organotriphosphate compound;

R_1 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl;

R_2 and R_3 are each independently selected from halo and C_{1-6} alkyl;

R_4 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl;

R_{5a} is selected from H, $-NH_2$, -OH, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl, wherein up to three methylene units of the C_{1-8} alkyl are optionally and independently replaced with –O-, NR'-, -C(O)-, -C(O)O-, and -C(O)NR'-, wherein R_{5a} is optionally substituted with up to three substituents selected from halo, CN, OH, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', $C(O)NR'_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, and C_{3-6} heteroaryl;

R_{5b} is H or C_{1-6} alkyl; or

R_{5a} and R_{5b} together with the nitrogen to which they are attached form a C_{3-6} heterocycloalkyl optionally substituted with halo, CN, OH, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', $C(O)NR'_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, or C_{3-6} heteroaryl;

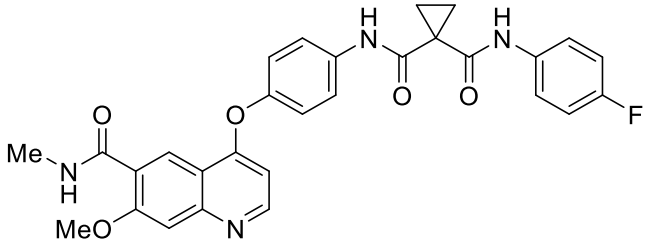
R_{5c} is H or C_{1-6} alkyl optionally substituted with halo, CN, OH, NH_2, or OR';

R' is H or C_{1-6} alkyl, and

w, x, y, and z are each independently an integer from 0 to 4;

and wherein the process optionally further comprises contacting the compound of Formula I with an acid to produce a pharmaceutically acceptable salt of the compound of Formula I.

[0007] In another example, the present disclosure includes a process for the preparation of Compound 1 (N-(4-fluorophenyl)-N-(4-((7-methoxy-6-(methylcarbamoyl)quinolin-4-yl)oxy)phenyl) cyclopropane-1,1-dicarboxamide):



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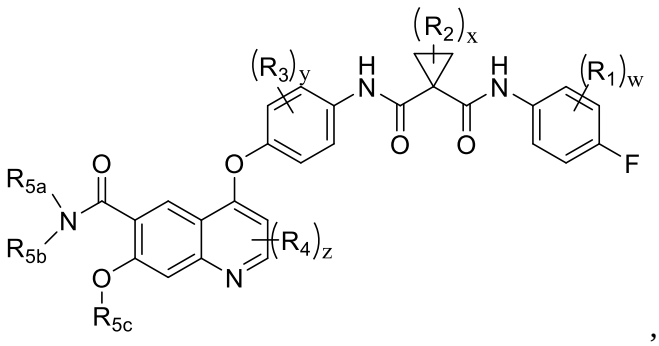
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4

What is claimed is:

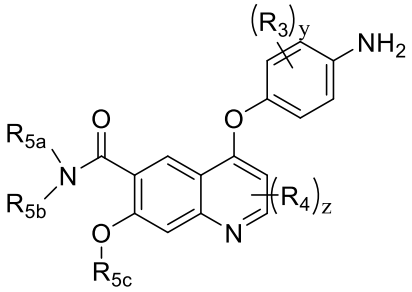
1. A process for preparing a compound of Formula I



,

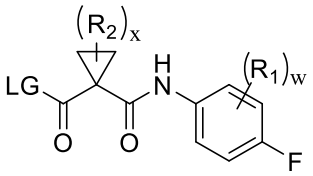
Formula I

or a pharmaceutically acceptable salt thereof, comprising contacting a compound of Formula II



Formula II

with a compound of Formula III



Formula III

in the presence of a solvent and a base, wherein

LG is a leaving group selected from Cl, Br, I, HOAt, HOBt, and an organotriphosphate compound;

R_1 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl;

R_2 and R_3 are each independently selected from halo and C_{1-6} alkyl;

R_4 is selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl;

R_{5a} is selected from H, OH, NH_2, C_{1-8} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, phenyl, and C_{3-6} heteroaryl, wherein the up to three methylene units of the C_{1-8} alkyl are optionally and independently replaced with –O-, NR'-, -C(O)-, -C(O)O-, and -C(O)NR'-, wherein R_{5a} is optionally substituted with up to three substituents selected from halo, CN, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', C(O)NR'$_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, and C_{3-6} heteroaryl;

R_{5b} is H or C_{1-6} alkyl; or

R_{5a} and R_{5b} together with the nitrogen to which they are attached form a C_{3-6} heterocycloalkyl optionally substituted with halo, CN, OH, NO_2, NH_2, SH, OR', C(O)OR', C(O)R', C(O)NR'$_2$, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, or C_{3-6} heteroaryl;

R_{5c} is H or C_{1-6} alkyl optionally substituted with halo, CN, OH, NH_2, or OR';

R' is H or C_{1-6} alkyl, and

w, x, y, and z are each independently an integer from 0 to 4;

and wherein the process optionally further comprises contacting the compound of Formula I with an acid to produce a pharmaceutically acceptable salt of the compound of Formula I.

2. The process of claim 1, wherein the base is an inorganic base selected from NaOH, Na_2CO_3, K_2CO_3, $NaHCO_3$, and $KHCO_3$, and the solvent is a mixture of water and an organic solvent selected from acetone, acetonitrile, butanediol, dimethylformamide, dimethoxyethane, dimethyl sulfoxide, 1,4-Dioxane, ethanol, ethylene glycol, furfuryl alcohol, glycerol, methanol, methyl isocyanide, N-methyl-2-pyrrolidone, 1-propanol, 1,3-propanediol, 1,5-pentanediol, 2-propanol, propylene glycol, tetrahydrofuran, and triethylene glycol.

3. The process of claim 1 or 2, wherein the solvent is a mixture of water and tetrahydrofuran, such as from approximately 2:1 tetrahydrofuran:water to approximately 3:1 tetrahydrofuran:water.

4. The process of any one of claims 1-3, wherein contacting a compound of Formula II with a compound of Formula III comprises adding a solution of the compound of Formula III dissolved in a first solvent to a solution of the compound of Formula II dissolved in a second solvent, to create a reaction mixture.

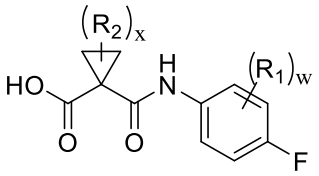
5. The process of claim 4, wherein the first solvent is an organic solvent such as tetrahydrofuran, and the second solvent is approximately 2:1 tetrahydrofuran:water, and wherein the compound of Formula III dissolved in a first solvent is added to a solution of a compound of Formula II dissolved in a second solvent over a period of at least 30 minutes.

6. The process of claim 4, wherein the reaction mixture is maintained at a temperature at approximately 20 to 25 ºC then heated to 35-40 °C and let stand to separate to an organic phase and an aqueous phase, followed by discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C.

7. The process of claim 6, further comprising adding water to the organic phase to create a second mixture while maintaining a temperature of 50-55 °C over a period of at least one hour, wherein the second mixture is stirred for at least 2 hours, and a solid product is obtained.

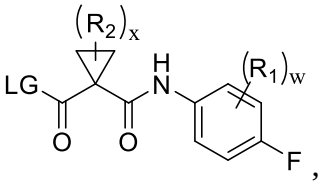
8. The process of any one of claims 1-7, wherein LG is Cl.

9. The process of claim 8, further comprising reacting a compound of Formula IV



Formula IV

with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride to produce the compound of Formula III



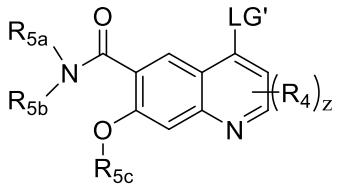
Formula III

wherein LG is Cl.

10. The process of claim 9, wherein the reagent is oxalyl chloride.

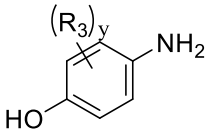
11. The process of claim 9, wherein reacting a compound of Formula IV with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed in the presence of a catalytic amount of dimethylformamide and an organic solvent such as tetrahydrofuran at a temperature of 15 ºC or less, such as a temperature between 5 and 15 ºC.

12. The process of any one of claims 1-11, further comprising reacting a compound of Formula V



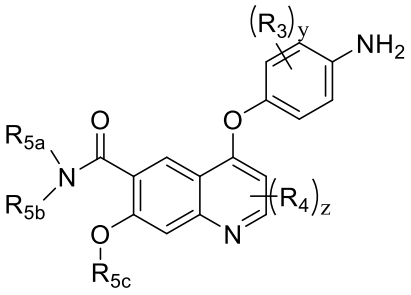
Formula V

with a compound of Formula VI

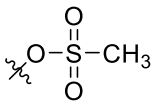
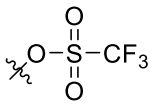
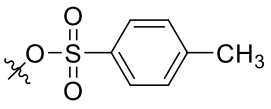


Formula VI

to provide the compound of Formula II



Formula II

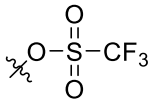
wherin LG' is selected from F, Cl, Br, I, , , , and $-N_2^+$.

13. The process of claim 12, wherein reacting a compound of Formula V with a compound of Formula VI is performed in the presence of a solvent such as an organic solvent selected from

acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, hexamethylphosphoric triamde (HMPT), tetrahydrofuran, 1,4-dioxane, and dichloromethane, and in the presence of a base selected from the group consisting of sodium *t*-pentoxide, n-BuLi, lithium diisopropyl amide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, sodium hydroxide, sodium methoxide, sodium *t*-butoxide, lithium hydroxide, lithium methoxide, lithium *t*-butoxide, lithium *t*-pentoxide, potassium hydroxide, potassium methoxide, potassium *t*-butoxide, potassium *t*-pentoxide, cesium hydroxide, cesium methoxide, cesium *t*-butoxide, and cesium *t*-pentoxide.

14. The process of claim 13, wherein the organic solvent is dimethylacetamide and the base is sodium *t*-pentoxide.

15. The process of any one of claims 12-14, wherein reacting a compound of Formula V with a compound of Formula VI is performed at a temperature of 75 to 80 ºC and the compound of Formula II is isolated by adding water to the reaction mixture and isolating the solid compound of Formula II.

16. The process of any one of claims 1-15, wherein LG' is selected from F, Cl, Br, and  such as Cl;

R_1 is selected from halo, methyl, methoxy, isopropoxy, and cyclopropyl;

w is 0, 1, or 2 such as 0;

x is 0;

R_3 is F or Cl;

y is 0, 1, or 2 such as 0;

R_4 is halo or C_{1-6} alkyl;

z is 0 or 1 such as 0

R_{5b} is H;

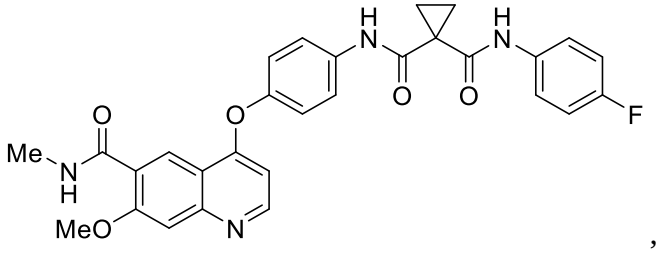
R_{5a} is selected from H, $-NH_2$, -OH, C_{1-6} alkyl, and C_{3-6} heterocycloalkyl, wherein the up to three methylene units of the C_{1-6} alkyl are optionally and independently replaced with –O- or NR'-, wherein R_{5a} is optionally substituted with up to three substituents selected from OH, C_{1-4}

alkyl, and C_{3-6} heterocycloalkyl, such as R_{5a} that is selected from H, -NH_2, -OH, methoxy, methyl, ethyl, N-methylazetidine-2-yl, pyrrolidine-2-yl-methyl, oxetane-2-yl-oxy, 2-hydroxyethyloxy, 2,3-dihydroxypropyloxy, oxetane-2-yl, 2-(N-piperidyl)ethyl, 2-(N-morpholino)ethyl, and 2-dimethylaminoethyl;

or R_{5a} and R_{5b} together with the nitrogen to which they are attached form a C_{3-6} heterocycloalkyl optionally substituted with OH such as R_{5a} and R_{5b} together with the nitrogen to which they are attached form azetidine or 2-hydroxyazetidine; and

R_{5c} is H or C_{1-6} alkyl optionally substituted with OR' such as methyl, 2-hydroxyethyl, 2-methoxyethyl, or 2-hydroxypropyl.

17. A process for preparing Compound 1



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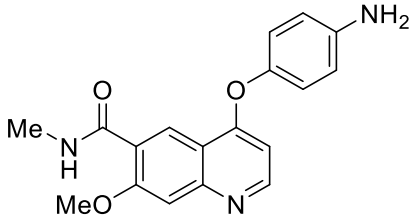
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4



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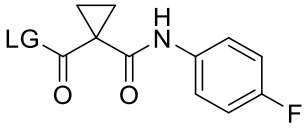
with a compound of Formula III'

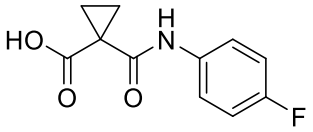


Formula III'

in the presence of a solvent and a base, wherein LG is a leaving group selected from Cl, Br, I, HOAt, HOBt, and an organotriphosphate compound, and wherein the process optionally further comprises contacting the compound of Compound 1 with an acid to produce a pharmaceutically acceptable salt of the compound of Compound 1.

18. The process of claim 17, wherein the process is conducted according to any one of claims 2-8.

19. The process of claim 17 or 18, further comprising reacting Compound 6



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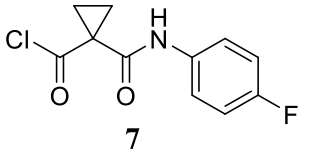
with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride to produce Compound 7



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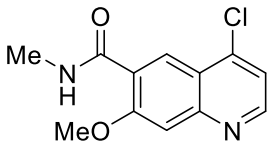
20. The process of claim 19, wherein the reagent is oxalyl chloride and the process is performed in the presence of a catalytic amount of dimethylformamide and an organic solvent such as tetrahydrofuran at a temperature of 15 ºC or less, such as a temperature between 5 and 15 ºC.

21. The process of any one of claims 17-20, further comprising reacting Compound 3



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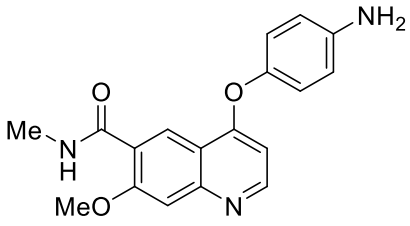
with 4-aminophenol (5) to provide Compound 4



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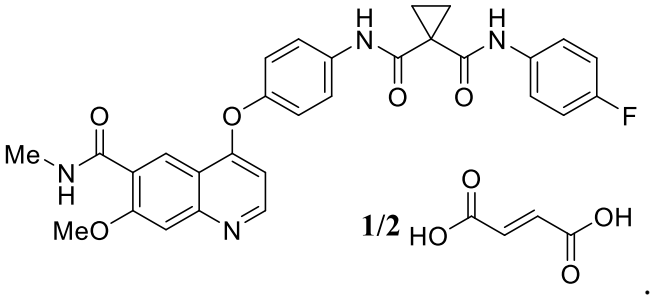
22. The process of claim 21, wherein the process is conducted according to any one of claims 13-18.

23. The process of any one of claims 17-22, further comprising reacting Compound 1 with fumaric acid to provide Compound 1-hemifumarate



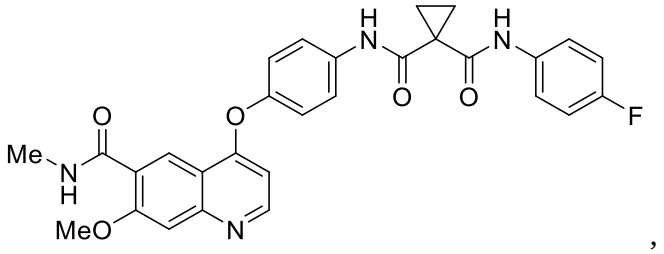
Compound 1-hemifumarate

24. The process of claim 23, wherein reacting Compound 1 with fumaric acid is performed in the presence of a solvent selected from water, an alcoholic solvent, THF, DMF, MEK, acetonitrile, 1,4-dioxane, and MTBE, or any combination thereof.

25. The process of claim 24, wherein the solvent is a mixture of water in an alcoholic solvent selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, pentanol, hexanol, heptanol, and octanol, such as that the solvent is a 20% solution of water in ethanol.

26. The process of any one of claims 23-25, wherein reacting Compound 1 with fumaric acid comprises adding a mixture of fumaric acid dissolved in the solvent of 20% solution of water in ethanol at 45-50 ºC to Compound 1 to create a reaction mixture, and further comprises heating the reaction mixture to reflux and stirring the reaction mixture for 4-6 hours at reflux, and cooling the reaction mixture and separating the Compound 1-hemifumarate from the solvent.

27. A process for preparing Compound 1



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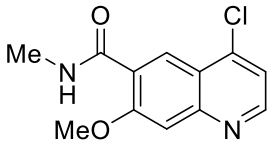
or a pharmaceutically acceptable salt thereof, comprising:

reacting Compound 3



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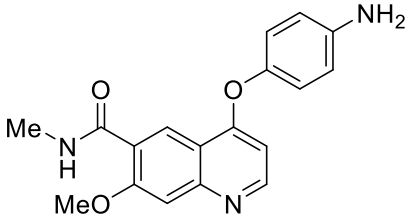
with 4-aminophenol (5) in the presence of dimethylacetamide and sodium *t*-pentoxide, at a temperature that is from 75 to 80 ºC, to provide a first reaction mixture comprising Compound 4



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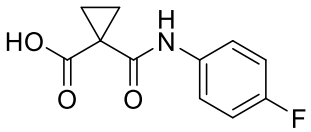
;

precipitating and isolating Compound 4 as a solid by adding water to the first reaction mixture;

reacting Compound 6



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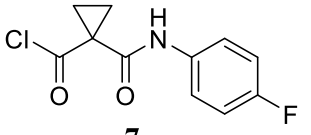
with oxalyl chloride in the presence of tetrahydrofuran and a catalytic amount of dimethylformamide at a temperature that is from 5 to 15 ºC to produce a second reaction mixture comprising Compound 7



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;

adding the second reaction mixture to a third reaction mixture comprising a solvent that is approximately 2:1 tetrahydrofuran:water, a base that is K_2CO_3, and Compound 4, over a period of at least 30 minutes to create a fourth reaction mixture wherein the temperature of the fourth reaction mixture is maintained below approximately 27 ºC during the addition;

heating the fourth reaction mixture to to 35-40 °C and letting stand to separate to an organic phase and an aqueous phase;

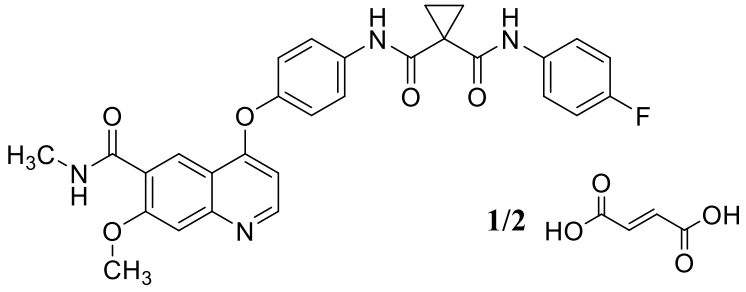
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

adding water to the organic phase over a period of at least one hour to create a fifth reaction mixture;

stirring the fifth reaction mixture for at least 2 hours; and

isolating Compound 1 as a solid product, and wherein the process optionally further comprises contacting the compound of Compound 1 with an acid to produce a pharmaceutically acceptable salt of the compound of Compound 1.

28. A process for preparing Compound 1-hemifumarate



Compound 1-hemifumarate

comprising:

adding a mixture of fumaric acid dissolved in a solvent of 20% solution of water in ethanol at 45-50 ºC to Compound 1 to create a reaction mixture;

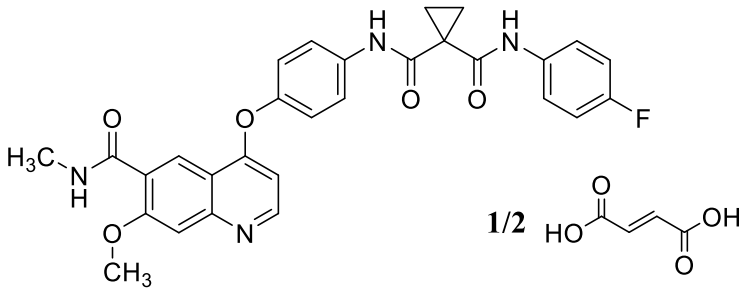
heating the reaction mixture to reflux;

stirring the reaction mixture at reflux for 4-6 hours;

cooling the reaction mixture; and

filtering the reaction mixture to obtain Compound 1·hemifumarate as a solid.

29. A process for preparing Compound 1-hemifumarate



Compound 1-hemifumarate

comprising:

combining a fumaric acid solution with Compound 1 to generate a reaction mixture comprising a slurry;

heating the reaction mixture to reflux for a predetermined amount of time; and

isolating Compound 1·hemifumarate as a solid.

30. The process of claim 29, wherein combining comprises adding the fumaric acid solution to Compound 1, wherein fumaric acid is dissolved in a mixed solvent of EtOH and acetone at about 45-50 ºC to form the fumaric acid solution, wherein the predetermined amount of time is between about 1 and 6 hours, and wherein isolating comprises cooling the reaction mixture comprising the slurry; filtering the reaction mixture to obtain a solid; and washing the solid.