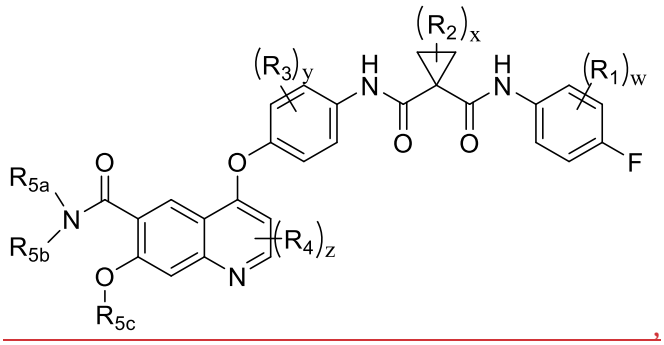
[0005] Therefore, a need exists for compounds, and processes of producing the compounds in high yield and purity, that inhibit TAM receptor tyrosine kinases such as Axl and Mer for the treatment of selected cancers.

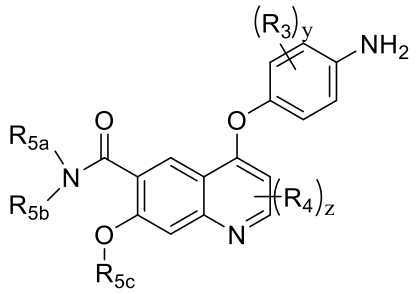
SUMMARY ~~OF THE INVENTION~~

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



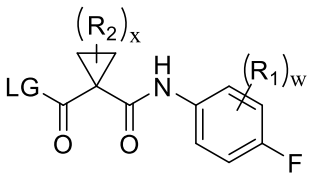
Formula I

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;

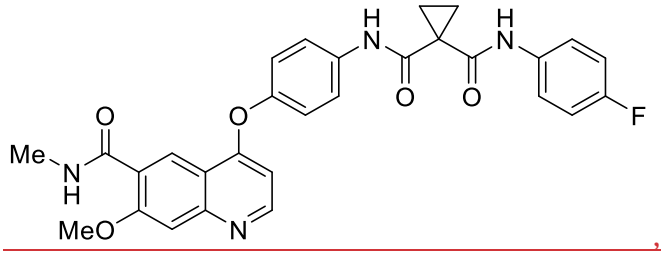
R_{5c} is H or C_{1-6} alkyl optionally substituted with halo, CN, OH, NH_2, or OR';

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

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

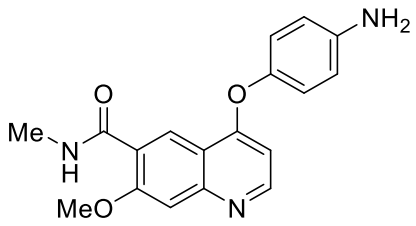
and wherein the process optionally further comprises contacting the compound of Formula I with an acid to produce a pharmaceutically acceptable salt of the compound of Formula I.

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



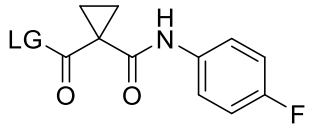
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4



4

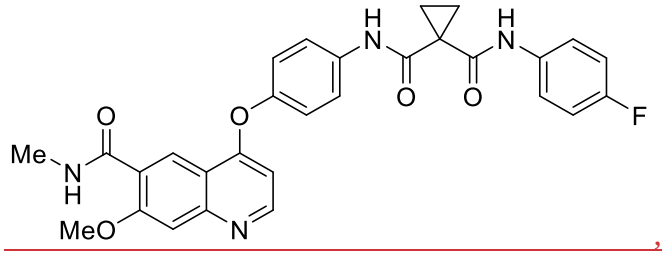
with a compound of Formula III'



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

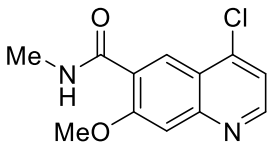


,

1

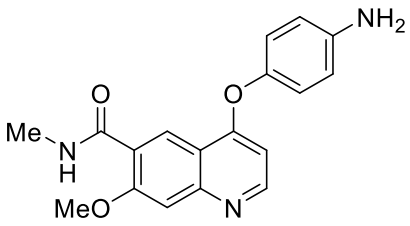
or a pharmaceutically acceptable salt thereof, comprising:

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

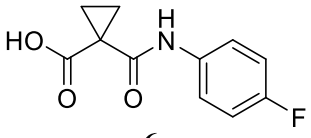


4

;

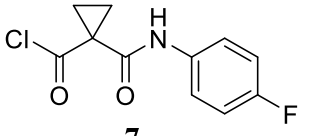
precipitating and isolating Compound 4 as a solid by adding water to the first reaction mixture;

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;

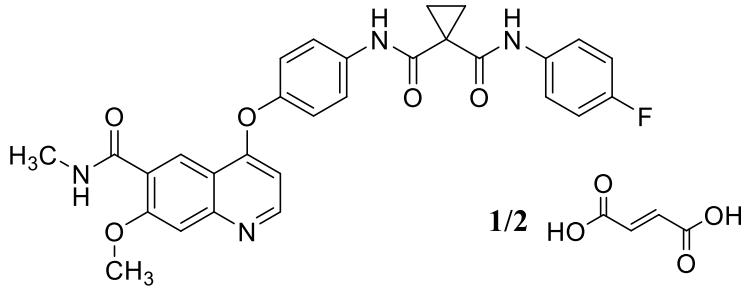
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

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;

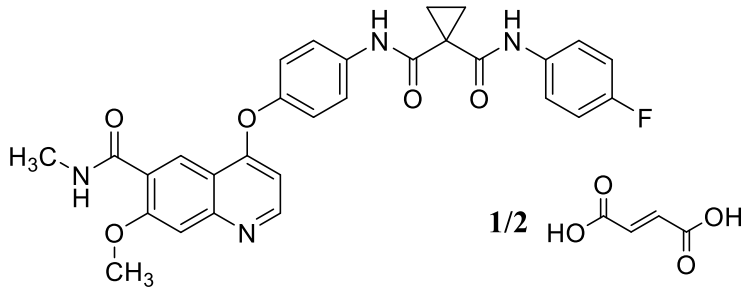
heating the reaction mixture to reflux;

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

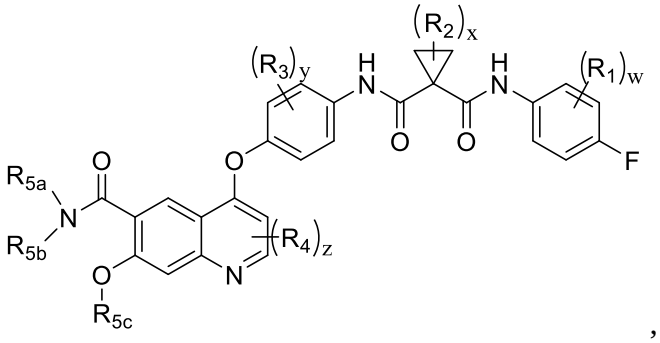
comprising:

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 ~~aspect~~example, the ~~invention~~ present disclosure includes a process for the preparation of a compound of Formula I



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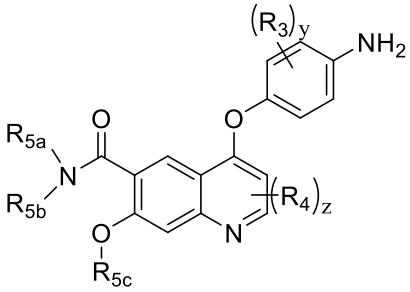
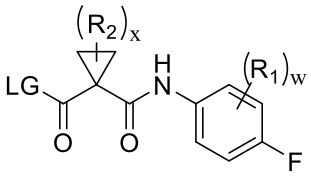
Formula I

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;

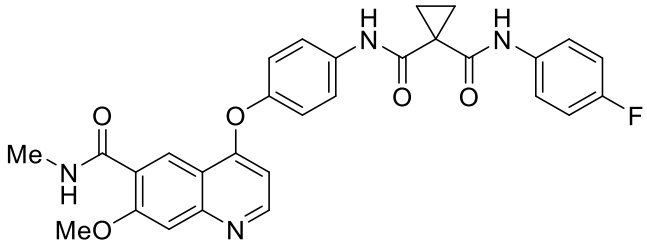
R_{5c} is H or C_{1-6} alkyl optionally substituted with halo, CN, OH, NH_2, or OR';

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 ~~aspect~~example, the present disclosure~~invention~~ 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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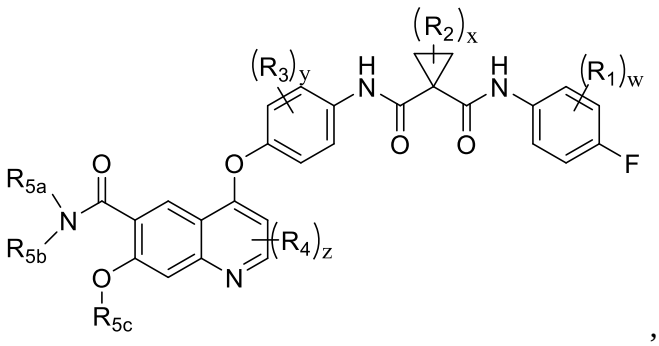
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4

What is claimed is:

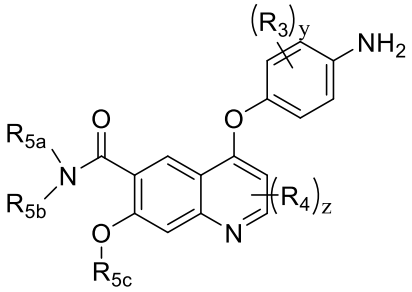
1. A process for preparing a compound of Formula I



,

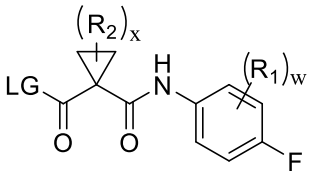
Formula I

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~~.~~

~~3. The process of claim 1 or claim 2, wherein the base is~~ selected from NaOH, Na_2CO_3, K_2CO_3, $NaHCO_3$, and $KHCO_3$~~.~~,

~~4. The process of any one of claims 1-3, wherein the base is K_2CO_3.~~

~~5. The process of any one of claims 1-4, wherein~~ and the solvent is a mixture of water and an organic solvent~~.~~

~~6. The process of claim 5, wherein the organic solvent is~~ 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.

~~7. The process of claim 6, wherein the organic solvent is selected from acetone, acetonitrile, dimethylformamide, 1,4-Dioxane, and tetrahydrofuran.~~

~~8.~~3. The process of ~~any one of~~ claim~~s 5-7~~ 1 or 2, wherein the solvent is a mixture of water and tetrahydrofuran~~.~~, such as

~~9. The process of any one of claim 8, wherein the mixture is~~ from approximately 2:1 tetrahydrofuran:water to approximately 3:1 tetrahydrofuran:water.

~~10.~~4. The process of any one of claims 1-~~3~~9, 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.

~~11.~~5. The process of claim ~~4~~10, wherein the first solvent is an organic solvent~~.~~

~~12. The process of claim 11, wherein the first solvent is~~ such as tetrahydrofuran~~.~~.

~~13. The process of claim 10, wherein~~ and the second solvent is approximately 2:1 tetrahydrofuran:water~~.~~.

~~14. The process of claim 10,~~ 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.

~~15.~~6. The process of claim ~~4~~10, wherein the reaction mixture is maintained at a temperature at approximately 20 to 25 ºC~~.~~

~~16. The process of claim 10, wherein the reaction mixture is~~ then heated to 35-40 °C and let stand to separate to an organic phase and an aqueous phase~~.~~.

~~17.~~ ~~The process of claim 16, further comprising~~ followed by discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C.

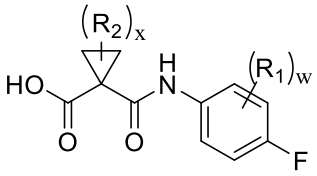
~~18.~~7. The process of claim ~~6~~17, further comprising adding water to the organic phase to create a second mixture while maintaining a temperature of 50-55 °C~~.~~

~~19.~~ ~~The process of claim 18, wherein the water is added to the organic phase~~ over a period of at least one hour~~.~~.

~~20.~~ ~~The process of claim 19,~~ wherein the second mixture is stirred for at least ~~1~~2 hours, and a solid product is obtained.

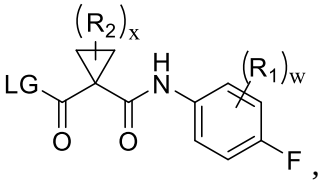
~~21.~~8. The process of any one of claims 1-~~7~~20, wherein LG is Cl.

~~22.~~9. The process of claim ~~8~~21, 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.

~~23.~~10. The process of claim ~~9~~22, wherein the reagent is oxalyl chloride.

~~24.~~11. The process of claim ~~9~~23, 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.

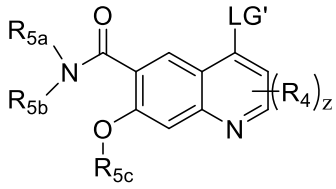
~~25. The process of any one of claims 22-24, wherein reacting a compound of Formula IV with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed in the presence of an organic solvent.~~

~~26. The process of claim 25, wherein the organic solvent is tetrahydrofuran.~~

~~27. The process of any one of claims 22-26, wherein reacting a compound of Formula IV with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed at a temperature of 15 ºC or less.~~

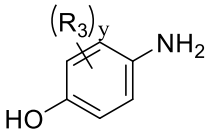
~~28. The process of any one of claims 22-27, wherein reacting a compound of Formula IV with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed at a temperature between 5 and 15 ºC.~~

~~29.~~12. The process of any one of claims 1-11~~28~~, further comprising reacting a compound of Formula V



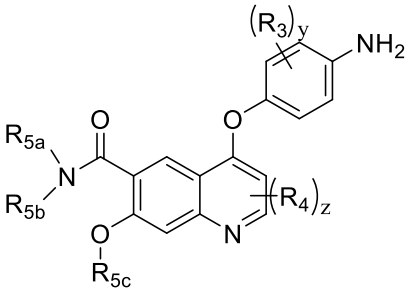
Formula V

with a compound of Formula VI



Formula VI

to provide the compound of Formula II



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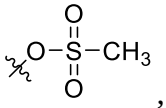
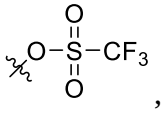
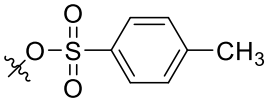
Formula II

wherin LG' is selected from F, Cl, Br, I, , , ,

and $-N_2^+$.

~~30.~~13. The process of claim 12~~29~~, wherein reacting a compound of Formula V with a compound of Formula VI is performed in the presence of a solvent~~.~~

~~31. The process of claim 30, wherein the solvent is~~ such as an organic solvent~~.~~

~~32. The process of claim 31, wherein the organic solvent is~~ selected from acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, hexamethylphosphoric triamde (HMPT), tetrahydrofuran, 1,4-dioxane, and dichloromethane~~.~~,

~~33. The process of claim 32, wherein the organic solvent is dimethylacetamide.~~

~~34. The process of any one of claims 29-33, wherein the reaction is performed~~ and in the presence of a base~~.~~

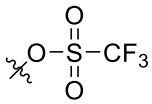
~~35. The process of claim 34, wherein the base is~~ selected from the group consisting of sodium *t*-pentoxide, n-BuLi, lithium diisopropyl amide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, sodium hydroxide, sodium methoxide, sodium *t*-butoxide~~, sodium *t*-pentoxide~~, lithium hydroxide, 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~~or~~ cesium *t*-pentoxide.

~~36.~~14. The process of claim 13~~35~~, wherein the organic solvent is dimethylacetamide and the base is sodium *t*-pentoxide.

~~37.~~15. The process of any one of claims ~~29-36~~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~~.~~

~~38. The process of any one of claims 29-37, wherein~~ and the compound of Formula II is isolated by adding water to the reaction mixture and isolating the solid compound of Formula II.

~~39.~~16. The process of any one of claims ~~29-38~~1-15, wherein LG' is selected from F, Cl, Br, and



such as ~~.~~

~~40. The process of claim 39, wherein LG' is~~ Cl;~~.~~

~~41. The process of any one of claims 1-40, wherein~~ R_1 is selected from halo, methyl, methoxy, isopropoxy, and cyclopropyl;~~.~~

~~42. The process of any one of claims 1-41, wherein~~ w is 0, 1, or 2 such as 0;~~.~~

~~43. The process of claim 42, wherein w is 0.~~

~~44. The process of any one of claims 1-43, wherein~~ x is 0;~~.~~

~~45. The process of any one of claims 1-44, wherein~~ R_3 is F or Cl;~~.~~

~~46. The process of any one of claims 1-45, wherein~~ y is 0, 1, or 2 such as 0;~~.~~

~~47. The process of claim 46, wherein y is 0.~~

~~48. The process of any one of claims 1-47, wherein~~ R_4 is halo or C_{1-6} alkyl;~~.~~

~~49. The process of any one of claims 1-48, wherein~~ z is 0 or 1 such as 0~~.~~

~~50. The process of claim 49, wherein z is 0.~~

~~51. The process of any one of claims 1-50, wherein~~ R_{5b} is H;~~.~~

~~52. The process of any one of claims 1-51, wherein~~ 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,~~.~~

~~53. The process of claim 52, wherein~~ 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;~~.~~

~~54. The process of claim 53, wherein R_{5a} is methyl.~~

~~55. The process of any one of claims 1-54, wherein R_{5c} is H or C_{1-6} alkyl optionally substituted with OR'.~~

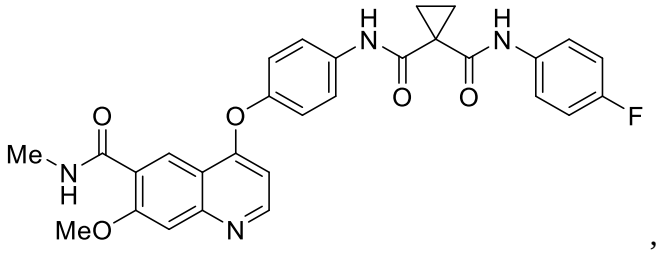
~~56. The process of claim 55, wherein R_{5c} is methyl, 2-hydroxyethyl, 2-methoxyethyl, or 2-hydroxypropyl.~~

~~57. The process of claim 56, wherein R_{5c} is methyl.~~

~~58. The process of any one of claims 1-50, wherein~~ 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~~.~~

~~59. The process of claim 58, wherein~~ 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.

~~60.~~17. A process for preparing Compound 1



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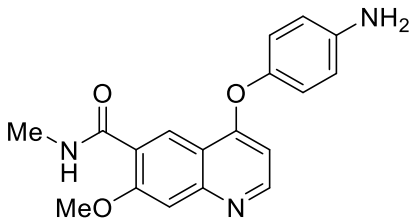
Compound 1

or a pharmaceutically acceptable salt thereof, comprising contacting Compound 4



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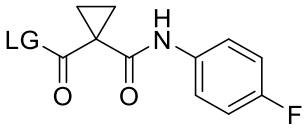
with a compound of Formula III'



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.

~~61.~~18. The process of claim 17~~60~~, wherein the process is conducted according to any one of claims 2-8 ~~base is an inorganic base~~.

~~62. The process of claim 60 or claim 61, wherein the base is selected from NaOH, Na_2CO_3, K_2CO_3, $NaHCO_3$, and $KHCO_3$.~~

~~63. The process of any one of claims 60-62, wherein the base is K_2CO_3.~~

~~64. The process of any one of claims 60-63, wherein the solvent is a mixture of water and an organic solvent.~~

~~65. The process of claim 64, wherein the organic solvent is 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.~~

~~66. The process of claim 65, wherein the organic solvent is selected from acetone, acetonitrile, dimethylformamide, 1,4-Dioxane, and tetrahydrofuran.~~

~~67. The process of any one of claims 64-66, wherein the solvent is a mixture of water and tetrahydrofuran.~~

~~68. The process of any one of claims 64-67, wherein the mixture is from approximately 2:1 tetrahydrofuran:water to approximately 3:1 tetrahydrofuran:water.~~

~~69. The process of any one of claims 60-68, wherein contacting Compound 4 with the compound of Formula III' comprises adding a solution of a compound of Formula III' dissolved in a first solvent to a solution of Compound 4 dissolved in a second solvent, to create a reaction mixture.~~

~~70. The process of claim 69, wherein the first solvent is an organic solvent.~~

~~71. The process of claim 70, wherein the first solvent is tetrahydrofuran.~~

~~72. The process of claim 69, wherein the second solvent is approximately 2:1 tetrahydrofuran:water.~~

~~73. The process of claim 69, wherein the compound of Formula III' dissolved in a first solvent is added to a solution of Compound 4 dissolved in a second solvent over a period of at least 30 minutes.~~

~~74. The process of claim 69, wherein the temperature of the reaction mixture is maintained at approximately 20 to 25 ºC.~~

~~75. The process of claim 69, wherein the reaction mixture is heated to 35-40 °C and let stand to separate to an organic phase and an aqueous phase.~~

~~76. The process of claim 75, further comprising discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C.~~

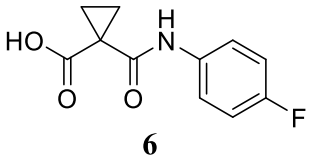
~~77. The process of claim 76, further adding water to the organic phase to create a second mixture while maintaining a temperature of 50-55 °C.~~

~~78. The process of claim 77, wherein the water is added to the organic phase over a period of at least one hour.~~

~~79. The process of claim 78, wherein the second mixture is stirred for at least 2 hours, and a solid product is obtained.~~

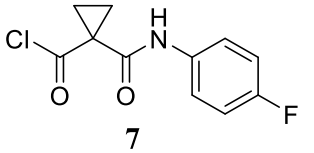
~~80. The process of any one of claims 60-79, wherein LG is Cl.~~

~~81.~~19. The process of claim 17 or 18~~80~~, further comprising reacting Compound 6



6

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



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~~82.~~20. The process of claim 19~~81~~, wherein the reagent is oxalyl chloride~~.~~

~~83. The process of claim 82, wherein the reaction~~ and the process is performed in the presence of a catalytic amount of dimethylformamide and an organic solvent~~.~~

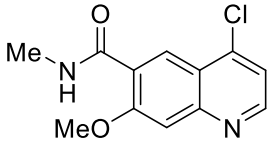
~~84. The process of any one of claims 81-83, wherein reacting Compound 6 with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed in the presence of an organic solvent.~~

~~85. The process of claim 84, wherein the organic solvent is~~ such as tetrahydrofuran~~.~~

~~86. The process of any one of claims 81-85, wherein the reacting Compound 6 with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed~~ at a temperature ~~that is~~of 15 ºC or less~~.~~.

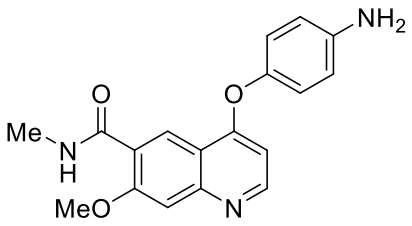
~~87. The process of any one of claims 81-86, wherein the reacting Compound 6 with a reagent selected from the group consisting of thionyl chloride and oxalyl chloride is performed at~~ such as a temperature between~~that is~~ 5 and ~~-~~15 ºC.

~~88.~~21. The process of any one of claims ~~60-87~~17-20, further comprising reacting Compound 3



3

with 4-aminophenol (5) to provide Compound 4



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~~89.~~22. The process of claim 21~~88~~, wherein ~~reacting Compound 3 with 4-aminophenol (5) is performed in the presence of a solvent~~the process is conducted according to any one of claims 13-18.

~~90. The process of claim 89, wherein the solvent is an organic solvent.~~

~~91. The process of claim 90, wherein the organic solvent is selected from acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, hexamethylphosphoric triamde (HMPT), tetrahydrofuran, 1,4-dioxane, and dichloromethane.~~

~~92. The process of claim 91, wherein the organic solvent is dimethylacetamide.~~

~~93. The process of any one of claims 88-92, wherein reacting Compound 3 with 4-aminophenol (5) is performed in the presence of a base.~~

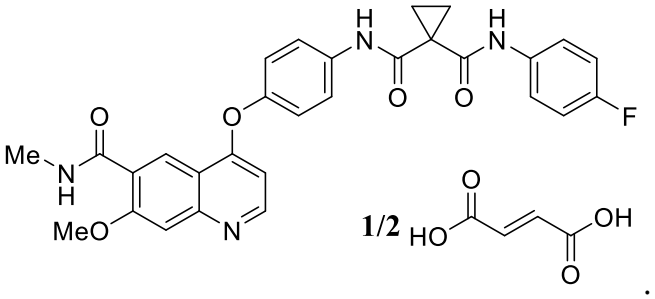
~~94. The process of claim 93, wherein the base is n-BuLi, lithium diisopropyl amide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, sodium hydroxide, sodium methoxide, sodium *t*-butoxide, sodium *t*-pentoxide, lithium hydroxide, lithium methoxide, lithium *t*-butoxide, lithium *t*-pentoxide, potassium hydroxide, potassium methoxide, potassium *t*-butoxide, potassium *t*-pentoxide, cesium hydroxide, cesium methoxide, cesium *t*-butoxide, or cesium *t*-pentoxide.~~

~~95. The process of claim 94, wherein the base is sodium *t*-pentoxide.~~

~~96. The process of any one of claims 88-95, wherein reacting Compound 3 with 4-aminophenol (5) is performed at a temperature of 75-80 ºC.~~

~~97. The process of any one of claims 88-96, further comprising adding water to the reaction mixture and isolating Compound 4 as a solid.~~

~~98.~~23. The process of any one of claims ~~60-97~~17-22, further comprising reacting Compound 1 with fumaric acid to provide Compound 1-hemifumarate



Compound 1-hemifumarate

~~99.~~24. The process of claim 23~~98~~, wherein reacting Compound 1 with fumaric acid is performed in the presence of a solvent~~.~~

~~100. The process of claim 99, wherein the solvent is~~ selected from water, an alcoholic solvent, THF, DMF, MEK, acetonitrile, 1,4-dioxane, and MTBE, or any combination thereof.

~~101.~~25. The process of claim 24~~100~~, wherein the solvent is a mixture of water in an alcoholic solvent~~.~~

~~102. The process of claim 101, wherein the alcoholic solvent is~~ selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, pentanol, hexanol, heptanol, and octanol,~~.~~

~~103. The process of claim 101, wherein~~ such as that the solvent is a 20% solution of water in ethanol.

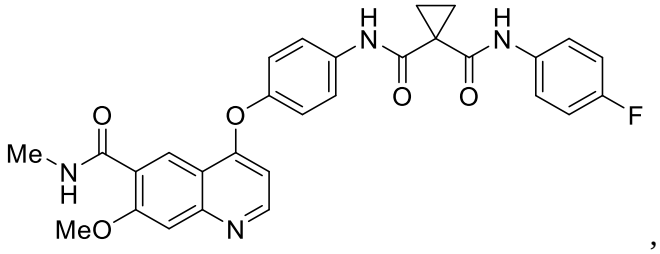
~~104.~~26. The process of any one of claims ~~98-103~~23-25, wherein reacting Compound 1 with fumaric acid comprises adding a mixture of fumaric acid dissolved in the solvent of 20% solution of water in ethanol at 45-50 ºC to Compound 1 to create a reaction mixture, and~~.~~

~~105. The process of claim 104,~~ further compris~~ing~~ heating the reaction mixture to reflux and stirring the reaction mixture~~.~~

~~106. The process of claim 105, wherein the reaction mixture is stirred~~ for 4-6 hours at reflux~~.~~, and

~~107. The process of claim 106, further comprising~~ cooling the reaction mixture and separating the Compound 1-hemifumarate from the solvent.

~~108.~~27. A process for preparing Compound 1



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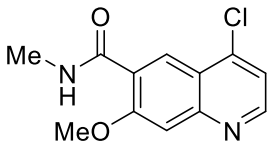
or a pharmaceutically acceptable salt thereof, comprising:

reacting Compound 3



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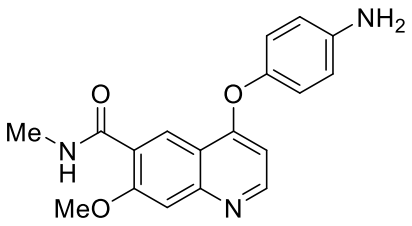
with 4-aminophenol (5) in the presence of dimethylacetamide and sodium *t*-pentoxide, at a temperature that is from 75 to 80 ºC, to provide a first reaction mixture comprising Compound 4



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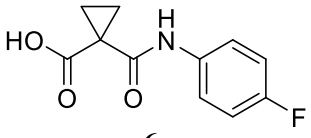
;

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

reacting Compound 6



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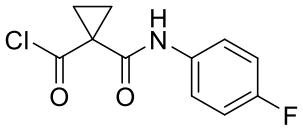
with oxalyl chloride in the presence of tetrahydrofuran and a catalytic amount of dimethylformamide at a temperature that is from 5 to 15 ºC to produce a second reaction mixture comprising Compound 7



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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;

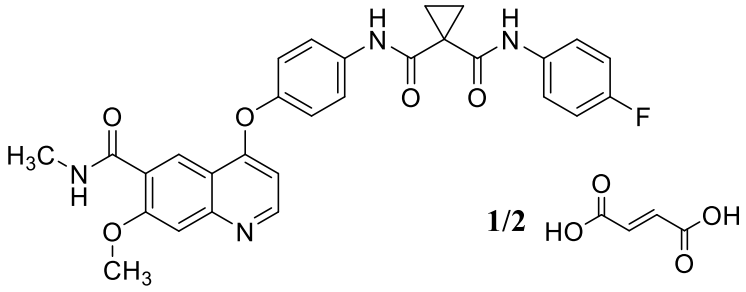
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

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.

~~109.~~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;

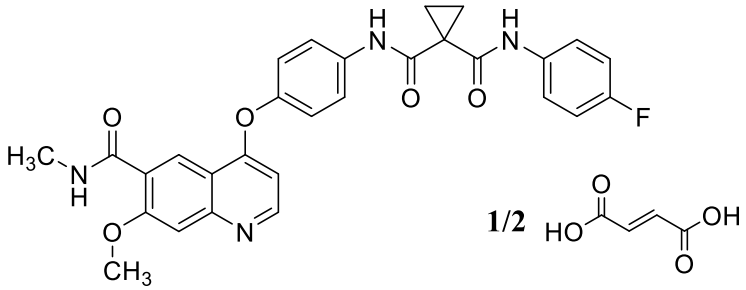
heating the reaction mixture to reflux;

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.

~~110.~~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.

~~111.~~30. The process of claim 29~~110~~, wherein combining comprises adding the fumaric acid solution to Compound 1,~~.~~

~~112. The process of claim 110,~~ wherein fumaric acid is dissolved in a mixed solvent of EtOH and acetone at about 45-50 ºC to form the fumaric acid solution,~~.~~

~~113. The process of claim 110,~~ wherein the predetermined amount of time is between about 1 and 6 hours,~~.~~

~~114. The process of claim 110,~~ and wherein isolating comprises cooling the reaction mixture comprising the slurry; filtering the reaction mixture to obtain a solid; and washing the solid.