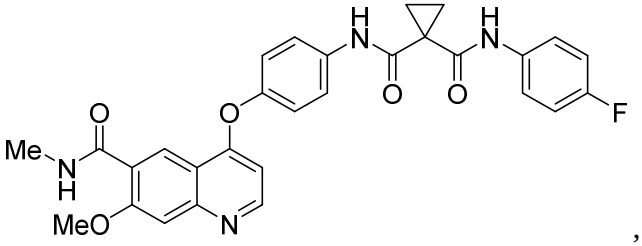
[0005] Therefore, a need exists for compounds, and processes of producing the compounds in high yield and purity, that inhibit TAM receptor tyrosine kinases such as Axl and Mer for the treatment of selected cancers.

SUMMARY

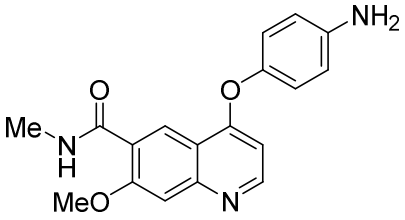
[0005a] In a first aspect of the present disclosure, there is provided a process for preparing Compound 1



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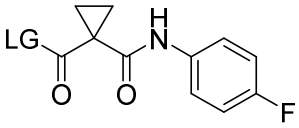
Compound 1

or a pharmaceutically acceptable salt thereof, the process comprising contacting Compound 4



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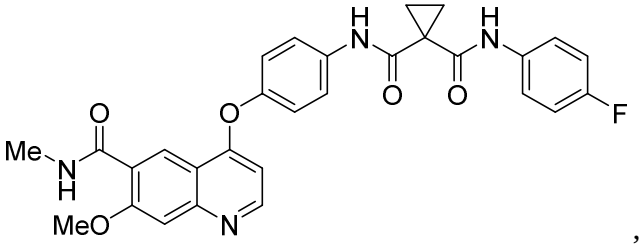
with a compound of Formula III'



Formula III'

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

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

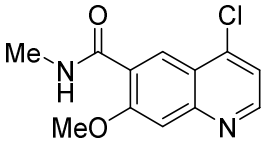


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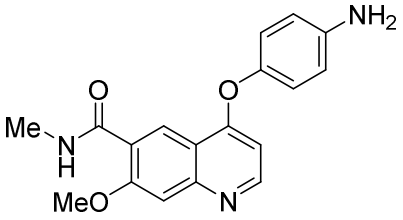
or a pharmaceutically acceptable salt thereof, the process comprising:

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

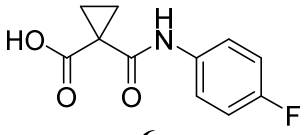


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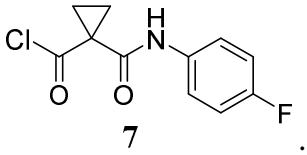
precipitating and isolating Compound 4 as a solid by adding water to the first reaction mixture;

reacting Compound 6



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 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 27 ºC during the addition;

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

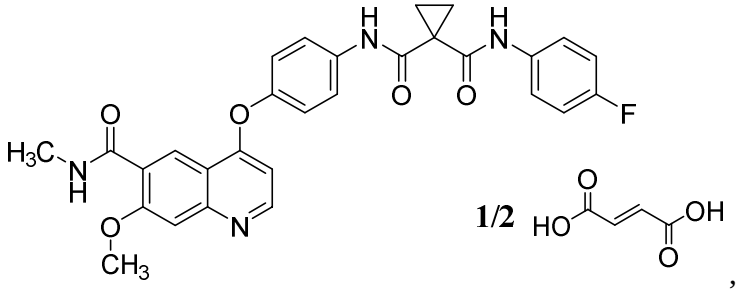
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

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, wherein the process optionally further comprises contacting Compound 1 with an acid to produce a pharmaceutically acceptable salt of Compound 1.

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

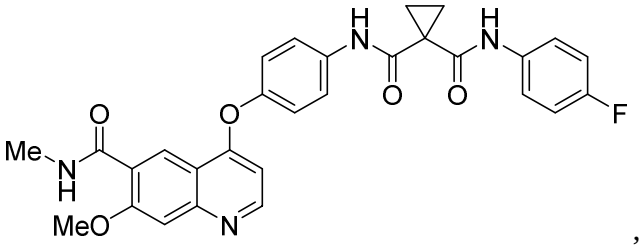


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Compound 1-hemifumarate

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



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to create a reaction mixture;

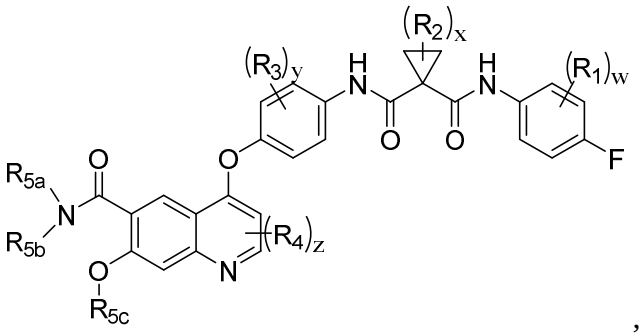
heating the reaction mixture to reflux;

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

cooling the reaction mixture; and

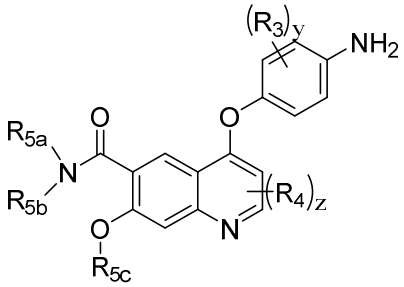
filtering the reaction mixture to obtain Compound 1·hemifumarate as a solid.

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



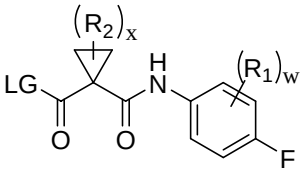
Formula I

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



Formula II

with a compound of Formula III



Formula III

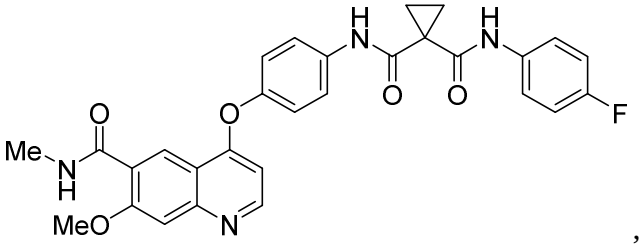
in the presence of a solvent and a base, wherein

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;

What is claimed is:

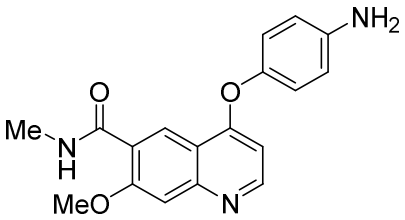
1. A process for preparing Compound 1



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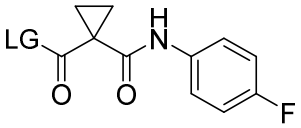
Compound 1

or a pharmaceutically acceptable salt thereof, the process 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, and I, and wherein the process optionally further comprises contacting Compound 1 with an acid to produce a pharmaceutically acceptable salt of Compound 1.

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.

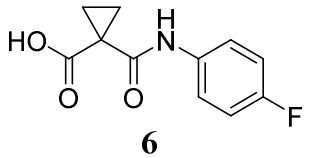
4. The process of claim 3, wherein the solvent is 2:1 tetrahydrofuran:water to 3:1 tetrahydrofuran:water.

5. The process of any one of claims 1-4, wherein contacting Compound 4 with the compound of Formula III' comprises adding a solution of the compound of Formula III' dissolved in tetrahydrofuran to a solution of Compound 4 dissolved in 2:1 tetrahydrofuran:water, to create a reaction mixture.

6. The process of claim 5, wherein the reaction mixture is maintained at a temperature at 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.

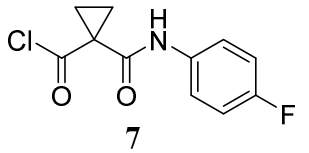
7. The process of claim 6, further comprising adding water to the organic phase to create a second mixture while maintaining a temperature of 50-55 °C over a period of at least one hour, wherein the second mixture is stirred for at least 2 hours, and a solid product is obtained.

8. The process of any one of claims 1-7, further comprising reacting Compound 6



6

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

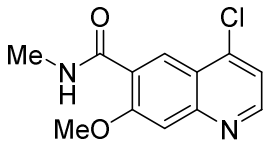


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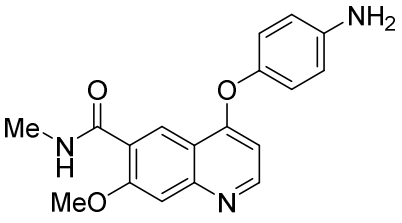
9. The process of claim 8, wherein the reagent is oxalyl chloride and the process is performed in the presence of a catalytic amount of dimethylformamide and an organic solvent tetrahydrofuran at a temperature between 5 and 15 ºC.

10. The process of any one of claims 1-9, further comprising reacting Compound 3



3

with 4-aminophenol (5) to provide Compound 4



4

.

11. The process of claim 10, wherein reacting Compound 3 with 4-aminophenol (5) is performed in the presence of an organic solvent selected from acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, hexamethylphosphoric triamde (HMPT), tetrahydrofuran, 1,4-dioxane, and dichloromethane.

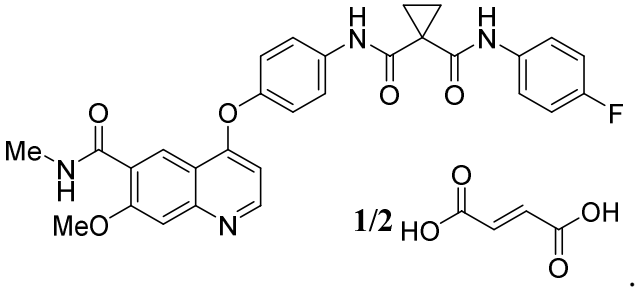
12. The process of claim 11, wherein the organic solvent is dimethylacetamide.

13. The process of any one of claims 10-12, wherein reacting Compound 3 with 4-aminophenol (5) is performed in the presence of a base selected from 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 cesium *t*-pentoxide.

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

15. The process of any one of claims 10-14, wherein reacting Compound 3 with 4-aminophenol (5) is performed at a temperature of 75-80 ºC and Compound 4 is isolated by adding water to the reaction mixture to afford the solid Compound 4.

16. The process of any one of claims 1-15, further comprising reacting Compound 1 with fumaric acid to provide Compound 1-hemifumarate



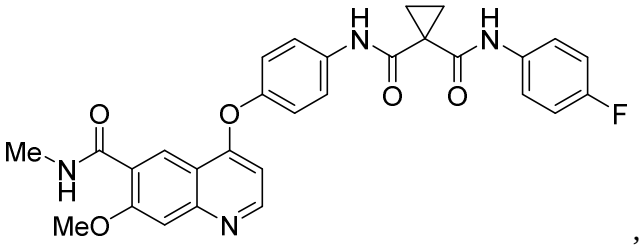
Compound 1-hemifumarate

17. The process of claim 16, 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.

18. The process of claim 17, wherein the solvent is a 20% solution of water in ethanol.

19. The process of any one of claims 16-18, 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.

20. A process for preparing Compound 1

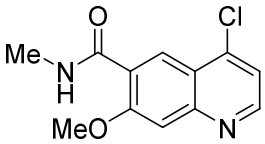


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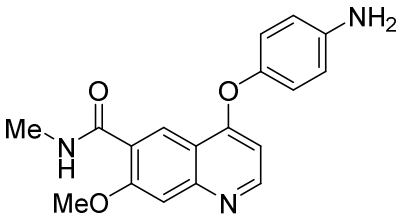
or a pharmaceutically acceptable salt thereof, the process comprising:

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

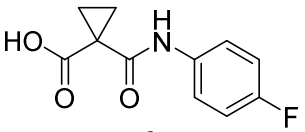


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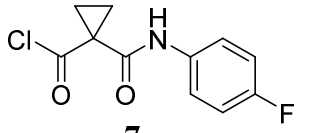
precipitating and isolating Compound 4 as a solid by adding water to the first reaction mixture;

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 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 27 ºC during the addition;

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

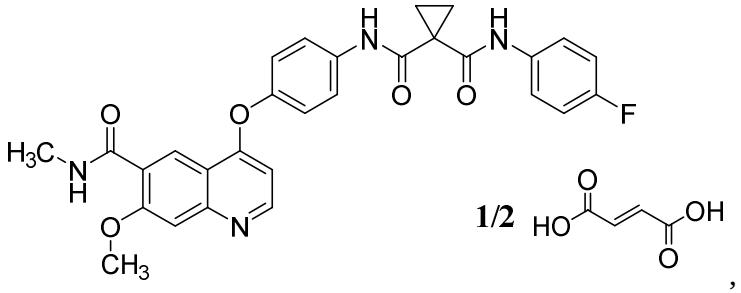
discarding the aqueous phase, heating the organic phase to 55-60 °C, and then filtering the organic phase at 55-60 °C;

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, wherein the process optionally further comprises contacting Compound 1 with an acid to produce a pharmaceutically acceptable salt of Compound 1.

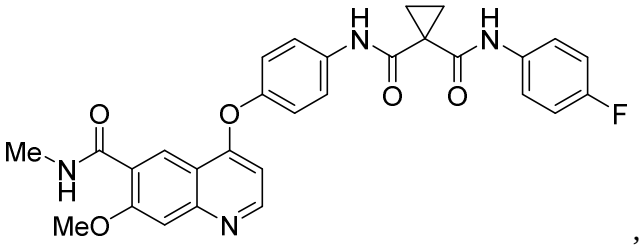
21. A process for preparing Compound 1-hemifumarate



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



,

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.