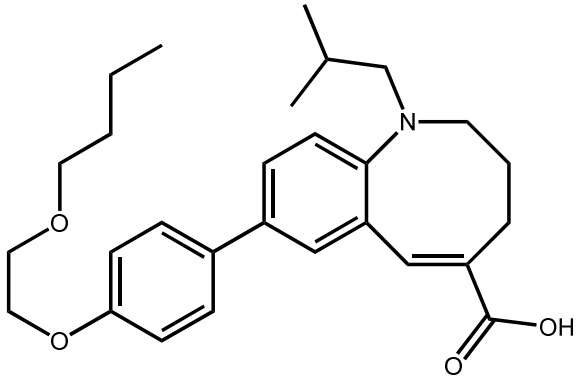
CLAIMS

What is claimed is:

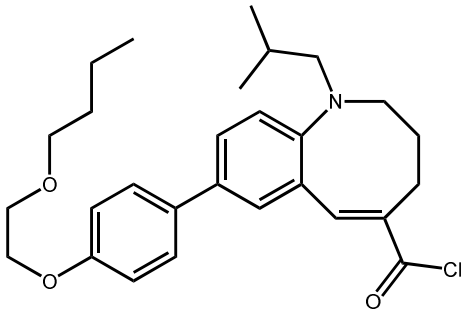
1. A process for preparing 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-N-(4-(((1-propyl-1H-imidazol-5-yl)methyl)sulfinyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate (Compound I-MsOH) comprising the steps of:

i) dissolving 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxylic acid (Compound II-OH) in a solvent, wherein the solvent comprises dichloromethane:



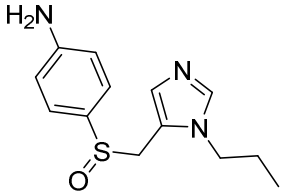
Compound II-OH ;

ii) adding a chlorinating reagent to step i), wherein the chlorinating reagent is selected from the group consisting of thionyl chloride, phosphorous trichloride, phosphorus pentachloride, phosphorus oxychloride, oxalyl chloride, phosgene, and a combination thereof to form (E)-8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-1,2,3,4-tetrahydrobenzo[b]azocine-5-carbonyl chloride (Compound II-Cl):



Compound II-Cl ;

a) reacting Compound II-Cl with 4-(((1-propyl-1*H*-imidazol-5-yl)methyl)sulfinyl)aniline (Compound III):



(III)

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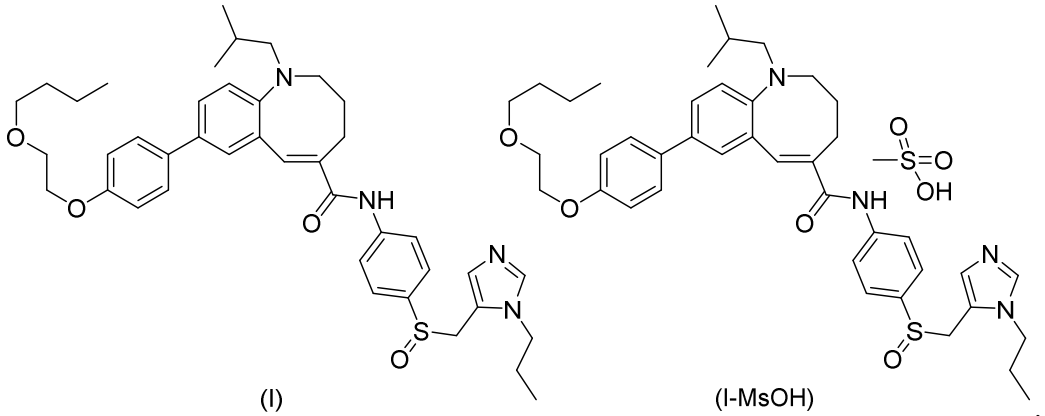
in the presence of a base to form 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-N-(4-(((1-propyl-1H-imidazol-5-yl)methyl)sulfinyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide (Compound I) in a solvent, wherein the solvent comprises dichloromethane;

b) quenching step a) with an aqueous solution;

c) adding methanesulfonic acid; and

d) crystallizing Compound I-MsOH to obtain crude Compound I-MsOH;



(I) (I-MsOH) .

2. The process of claim 1, wherein the base in step a) comprises pyridine.

3. The process of claim 1 or claim 2, wherein Compound III of step a) is optically pure (*S*)-Compound III.

4. The process of any one of claims 1 to 3, wherein Compound III is in the amount of about 1.0 to about 1.2 equivalent of 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxylic acid (Compound II-OH).

5. The process of any one of claims 1 to 4, wherein aqueous citric acid is present in step b).

6. The process of any one of claims 1 to 5, wherein step b) further comprises extracting Compound I and drying the extracted solution with 3 Å molecular sieves.

7. The process of any one of claims 1 to 6, wherein the acid in step c) is in the amount of about 0.97 to about 1.02 equivalent of 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxylic acid (Compound II-OH).

8. The process of any one of claims 1 to 7, wherein step d) further comprises seeding with Compound I-MsOH; stirring the mixture at about 0 ºC to obtain precipitated crystals; and washing collected precipitated crystals with chilled ethyl acetate.

9. The process of any one of claims 1 to 7, wherein after step d) further comprises the steps of:

i) dissolving the crude Compound I-MsOH obtained from step d) in acetonitrile at about 70 ºC;

ii) reducing the temperature of the mixture of step i) to about 50 ºC to about 55 ºC over about 1 hour;

iii) seeding step ii) with Compound I-MsOH;

iv) stirring at about 50 ºC to about 55 ºC for about 6 hours;

v) reducing the temperature of the mixture of step iv) to about 20 ºC;

vi) stirring at about 20 ºC for about 8 hours;

vii) collecting crystals by filtration; and

viii) washing filtered crystals with cold acetonitrile.

10. The process of claim 1, wherein the chlorinating reagent in step ii) is thionyl chloride.

11. The process of claim 1 or 10, wherein the chlorinating reagent is in an amount of about 1.0 to about 1.2 equivalent of 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxylic acid (Compound II-OH).

12. The process of claim 1, wherein 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-N-(4-(2-(1-propyl-1H-imidazol-5-yl)acetyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate (Compound I-MsOH) or an enantiomer, a stereoisomer, or a combinations thereof, has a purity of 96.0% or higher.

13. The process of claim 1, wherein 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-N-(4-(2-(1-propyl-1H-imidazol-5-yl)acetyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate (Compound I-MsOH) or an enantiomer, a stereoisomer, or a combinations thereof, has a purity of 98.5% or higher.

14. The process of claim 1, wherein 8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-N-(4-(2-(1-propyl-1H-imidazol-5-yl)acetyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate (Compound I-MsOH) is (*S*)-8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-*N*-(4-(((1-propyl-1*H*-imidazol-5-yl)methyl)sulfinyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate ((*S*)-Compound I-MsOH).

15. The process of claim 14, wherein (*R*)-8-(4-(2-butoxyethoxy)phenyl)-1-isobutyl-*N*-(4-(((1-propyl-1*H*-imidazol-5-yl)methyl)sulfinyl)phenyl)-1,2,3,4-tetrahydrobenzo[b]azocine-5-carboxamide methanesulfonate ((*R*)-Compound I-MsOH) is present in 0.5% or less.