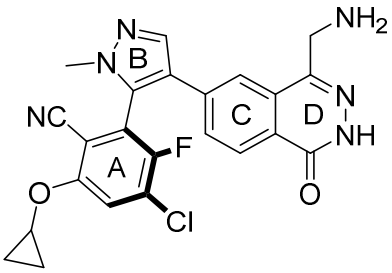
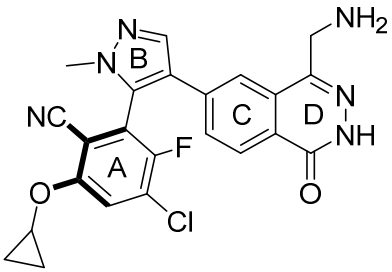
We claim:

1. A method of separating a mixture of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile (Compound *M-2*) and (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile (Compound *P-2*) enantiomers



Compound *M*-2



Compound *P*-2

the method comprising the steps of:

(a) contacting the mixture with *N*-Boc-*D*-phenylalanine to form a mixture of Compound *M*-2 *N*-Boc-*D*-phenylalanine salt and Compound *P-2 N*-Boc-*D*-phenylalanine salt;

(b) filtering the mixture to obtain a solid phase enriched with the Compound *M*-2 *N*-Boc-*D*-phenylalanine salt; and

(c) reacting the solid phase with excess NH_3, or other base, to obtain a solid enriched with *M*-enantiomer free base of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile .

2. The method of claim 1, wherein the contacting in step (a) occurs in MeOH or aqueous MeOH, or in EtOH or aqueous EtOH, or in THF or aqueous THF.

3. The method of any of claims 1-2, wherein the reaction of step (c) occurs in an iso-propyl alcohol solution, or isopropyl alcohol and water solution.

4. The method of any of claims 1-3, wherein filtrate from step (b) enriched with Compound *P*-2 *N*-Boc-*D*-phenylalanine salt is heated to obtain a racemic or nearly racemic mixture of Compound *P*-2 and Compound *M*-2.

5. The method of claim 4, wherein said mixture is separated to obtain pure or enriched Compound *M*-2 *N*-Boc-*D*-phenylalanine salt.

6. A method of separating a mixture of Compound *M*-2 and Compound *P*-2 enantiomers, the method comprising the steps of:

(a) contacting the mixture with *N*-Boc-*L*-phenylalanine to form a mixture of Compound *M*-2 *N*-Boc-*L*-phenylalanine salt and Compound *P*-2 *N*-Boc-*L*-phenylalanine salt;

(b) filtering the solid phase to obtain a liquid phase enriched with the Compound *M*-2 *N*-Boc-*L*-phenylalanine salt; and

(c) reacting the Compound *M*-2 *N*-Boc-*L*-phenylalanine salt with base to obtain a solid free base Compound *M*-2.

7. The method of claim 6, wherein the contacting in step (a) occurs in MeOH or aqueous MeOH, or in EtOH or aqueous EtOH, or in THF or aqueous THF.

8. The method of any of claims 1-7, wherein step (c) occurs in a suspension of water and dichloromethane, or step (c) occurs in other than a suspension of water and dichloromethane.

9. A method of obtaining substantially pure or enriched Compound *M*-2 , the method comprising the steps of:

(a) obtaining a mixture of Boc-protected Compound *M*-2 and Boc-protected Compound *P*-2;

(b) chromatographically separating the Boc-protected Compound *M*-2 from the Boc-protected Compound *P*-2; and

(c) deprotecting the Boc-protected Compound *M*-2.

10. A method for producing a sample containing a diastereomeric excess of Compound *M*-2, the method comprising heating a mixture having a first ratio of Compound *P*-2 *N*-Boc-*D*-phenylalanine salt to Compound *M*-2 *N*-Boc-*D*-phenylalanine salt to obtain a mixture having a second ratio of Compound *P*-2 *N*-Boc-*D*-phenylalanine salt to Compound *M*-2 *N*-Boc-D-phenylalanine salt.

11 A compound which is

the *N*-Boc-*D*-phenylalanine salt of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-*1H*-pyrazol-5-yl)-3-fluoro-3,4-dihydronaphthalene-1-carbonitrile;

the *N*-Boc-*D*-phenylalanine salt of (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-*1H*-pyrazol-5-yl)-3-fluoro-3,4-dihydronaphthalene-1-carbonitrile;

the *N*-Boc-*L*-phenylalanine salt of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-*1H*-pyrazol-5-yl)-3-fluoro-3,4-dihydronaphthalene-1-carbonitrile;

the *N*-Boc-*L*-phenylalanine salt of (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-*1H*-pyrazol-5-yl)-3-fluoro-3,4-dihydronaphthalene-1-carbonitrile;

the *N*-Boc-*D*-phenylalanine salt of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile;

the *N*-Boc-*D*-phenylalanine salt of (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile;

the *N*-Boc-*L*-phenylalanine salt of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile; or

the *N*-Boc-*L*-phenylalanine salt of (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile.

12. A crystalline form of *N*-Boc-*D*-phenylalanine salt of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile.

13. Crystalline Form A of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile; Crystalline Form A of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile hydrochloric acid salt; or Crystalline Form B

of (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile hydrochloric acid salt.

14. A method of separating a mixture of atropisomers, the method comprising:

(a) forming a mixture of a solvent, a first atropisomer and a second atropisomer in a crystallization vessel;

(b) producing a liquid phase and a solid phase by, if necessary, adjusting the temperature of the mixture to a temperature in which the first atropisomer and second atropisomer have different solubilities, where the solid phase contains an enantiomeric excess of the first atropisomer and the liquid phase contains an enantiomeric excess of the second atropisomer;

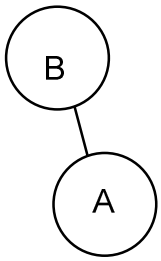
(c) removing a portion of the liquid phase;

(d) subjecting the removed liquid phase portion to conditions sufficient to produce an increased amount of the first atropisomer in the removed liquid phase relative to the amount in the liquid phase in (b);

(e) returning the removed liquid phase produced in (d) to the crystallization vessel; and

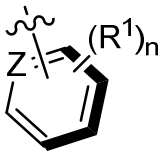
(f) isolating crystals of the first atropisomer.

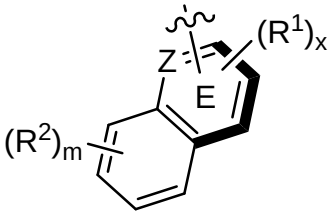
15. A method of separating a mixture of atropisomers according to claim 14, wherein the atropisomers are of a compound having the formula



wherein

the A-ring is



or


wherein the point of attachment of the bicyclic A-ring to the B-ring is on ring E; the B-ring is a 6-10 membered aryl group, 5-10 membered heteroaryl group, 5-10 membered heterocycloalkyl group, an amide group, a sulfone group, a sulfoxide group, an olefin group, an amine group, or an ether group, each of which is optionally substituted;

Z is N, CH or CR^1;

n is 0, 1, 2, 3, or 4;

x is 0, 1, or 2;

m is 0, 1, 2, 3 or 4;

each R^1 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyloxy, halogen, cyano, hydroxy, amino, or mono- or di-C_1-C_6 alkyl amino; and

each R^2 is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyloxy, halogen, cyano, hydroxy, amino, or mono- or di-C_1-C_6 alkyl amino;

provided that at least one of the positions on the A-ring ortho to the point of attachment of the A-ring to the B-ring is substituted with R^1.

16. A method of separating a mixture of atropisomers according to any one of claims 14-15, wherein the first atropisomer is (2*M*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile (Compound *M-2*) and the second atropisomer is (2*P*)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1*H*-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile (Compound *P-2*).

17. A method of separating a mixture of atropisomers according to any one of claims 14-16, wherein the subjecting in (d) comprises heating at a temperature of from about 80-200°C.

18. A method according to claim 1, wherein

the contacting generates a slurry comprising

a solid phase enriched with the Compound M-2 N-Boc-D-phenylalanine salt, and

a liquid phase enriched with the Compound P-2 N-Boc-D-phenylalanine salt; and

the method further comprises

separating a portion of the liquid phase from the slurry, and

heating the liquid phase to produce a heated mixture having a ratio of Compound P-2 N-Boc-D-phenylalanine salt to Compound M-2 N-Boc-D-phenylalanine salt that is different than the ratio prior to the heating.

19. A system for separating atropisomers comprising a crystallization module, an epimerization module and an optional collection module.

20. A method for separating atropisomers comprising

selectively crystallizing a less soluble atropisomer in a crystallization module; and

epimerizing a more soluble atropisomer in an epimerization module;

wherein soluble material is continuously or semi-continuously provided from the crystallization module directly or indirectly to the epimerization module, and material from the epimerization module is at least semi-continuously returned to the crystallization module.