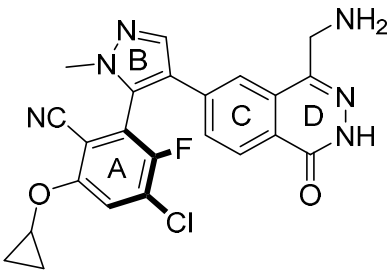
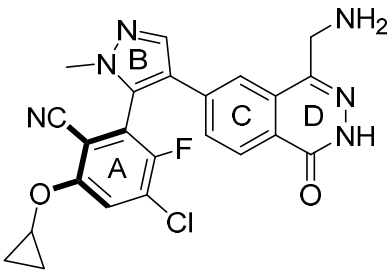
salt diastereomer (*P*-A*) is less soluble and preferentially crystallizes, consequently enriching the supernatant in Compound 2 salt *M*-A*.

[00012a] In one aspect, there is provided 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.

[00012b] In another aspect, the present disclosure provides 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.

[00012c] In yet another aspect, there is provided 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.

[00012d] In another aspect, there is provided 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.

[00013] The present disclosure also provides salts of Compound 1 and Compound 2. In particular, the invention provides

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; and

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.

[00014] The present disclosure further also encompasses solid forms of the above described Boc-phenylalanine salts, in particular 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.

[00015] The present disclosure also encompasses crystalline forms 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 and (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. More specifically, the disclosure provides 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, i.e., crystalline Form A of Compound M-2. The disclosure also provides crystalline Form A and 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.

[00016] The disclosure also provides systems for producing and isolating crystalline forms of (2M)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile and (2M)-2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile hydrochloric acid salt, in particular, 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.

[00016a] In a further aspect, there is provided 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.

[00016b] In yet another aspect of the present disclosure, there is provided a system for separating atropisomers comprising a crystallization module, an epimerization module and an optional collection module.

[00016c] In a further aspect, the present disclosure provides 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.

BRIEF DESCRIPTION OF THE FIGURES

[00017] **Fig. 1** is a flow chart showing the separation of highly enriched or pure Compound *M*-2 as a solid as described in Examples 1A and 1B.

[00018] **Fig. 2** is a flow chart showing the separation of highly enriched or pure Compound *M*-2 in the liquid phase as described in Example 2.

[00019] **Fig. 3** is a diagram of a system according to the invention that comprises a crystallization module and an epimerization module.

[00020] **Fig. 4** is a 1H qNMR analysis according to an example embodiment.