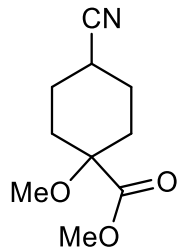
entitled “AcceleRET Lung Study of Pralsetinib for 1L RET Fusion-positive, Metastatic NSCLC” are underway.

[0005] Pralsetinib is disclosed as one of many RET inhibitor compounds in patent publication WO2017/079140. The successful commercialization of a new therapeutic agent requires an efficient process for preparing the agent in high yield and purity. Therefore, there still exists a need for improved processes for preparing pralsetinib that are more efficient and suitable for large scale manufacturing processes.

SUMMARY ~~OF THE DISCLOSURE~~

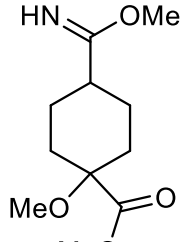
[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



(I),

or a salt thereof.

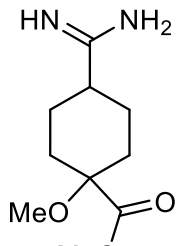
[0005b] In another aspect of the present disclosure, there is provided a compound of Formula (II):



(II),

or a salt thereof.

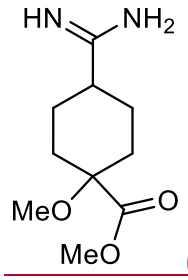
[0005c] In a further aspect of the present disclosure, there is provided a compound of Formula (III):



(III),

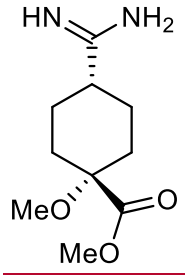
or a salt thereof.

[0005d] In another aspect of the present disclosure, there is provided an isomeric mixture of *cis* and *trans* isomers of a compound of Formula (III):



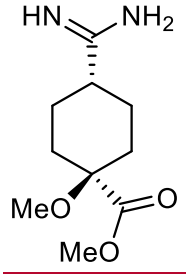
(III),

or a salt thereof, wherein the *cis* isomer is a compound of Formula (IIIa):



(IIIa),

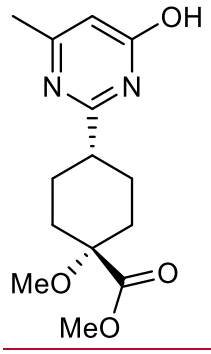
or a salt thereof, and the *trans* isomer is a compound of Formula (IIIb):



(IIIb),

or a salt thereof, wherein the ratio of the *cis* isomer to the *trans* isomer is greater than or equal to about 4 to 1.

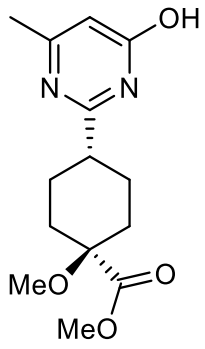
[0005e] In a further aspect of the present disclosure, there is provided a compound of Formula (Iva):



(Iva),

or a salt thereof.

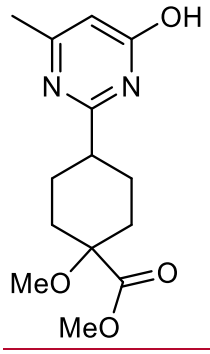
[0005f] In another aspect of the present disclosure, there is provided a compound of Formula (IVb):



(IVb),

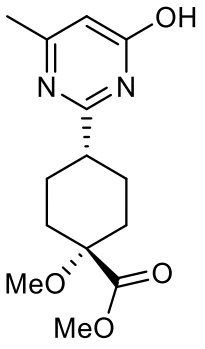
or a salt thereof.

[0005g] In a further aspect of the present disclosure, there is provided an isomeric mixture of *cis* and *trans* isomers of a compound of Formula (IV):



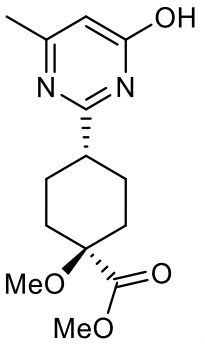
(IV),

or a salt thereof, wherein the *cis* isomer is a compound of Formula (IVa):



(IVa),

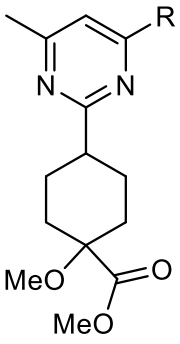
and the *trans* isomer is a compound of Formula (IVb):



(IVb),

or a salt thereof, wherein the ratio of the *cis* isomer to the *trans* isomer is greater than or equal to about 4 to 1.

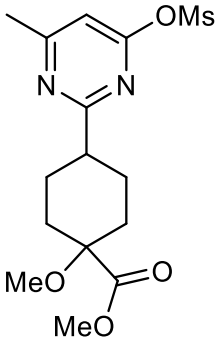
[0005h] In another aspect of the present disclosure, there is provided a compound of Formula V-1:



(V-1),

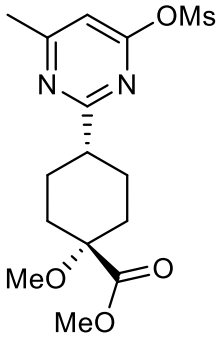
or a salt thereof, wherein R is an activating group.

[0005i] In a further aspect of the present disclosure, there is provided an isomeric mixture of *cis* and *trans* isomers of a compound of Formula (V):



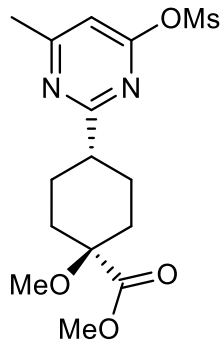
(V),

or a salt thereof, wherein the *cis* isomer is a compound of Formula (Va):



(Va),

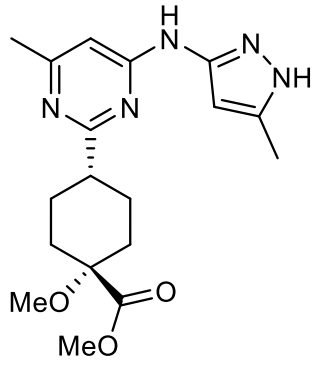
or a salt thereof, and the *trans* isomer is a compound of Formula (Vb):



(Vb),

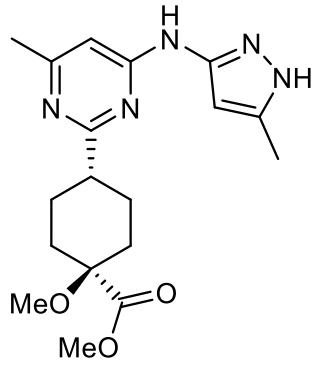
or a salt thereof, wherein the ratio of the *cis* isomer to the *trans* isomer is greater than or equal to about 4 to 1.

[0005j] In another aspect of the present disclosure, there is provided a composition comprising a compound of Formula VI:



(VI),

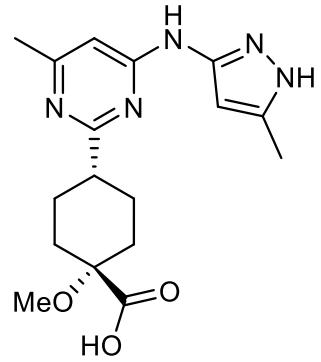
or a salt thereof, wherein the composition is substantially free of a compound of Formula (VIa):



(VIa),

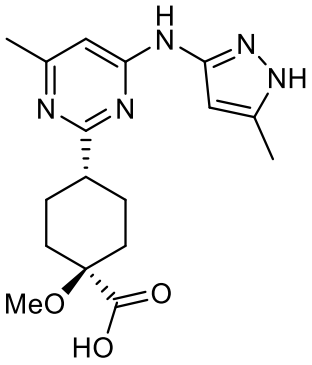
or a salt thereof.

[0005k] In a further aspect of the present disclosure, there is provided a composition comprising a compound of Formula (VII):



(VII),

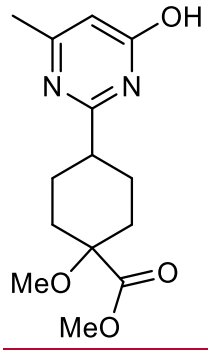
or a salt thereof, wherein the composition is substantially free of the compound of Formula (VIIa):



(VIIa),

or a salt thereof.

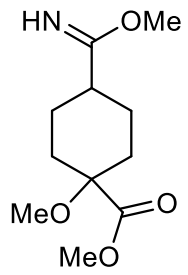
[0005l] In another aspect of the present disclosure, there is provided a process of preparing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (IV):



(IV),

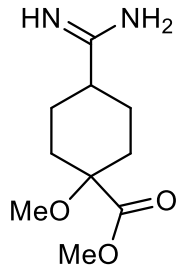
or a salt thereof, wherein the process comprises:

(a) reacting a compound of Formula (II):



(II),

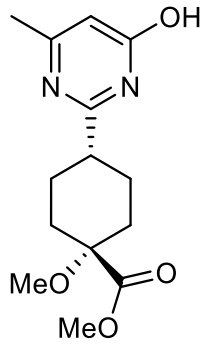
or a salt thereof with an ammonium source in the presence of a solvent, thereby producing a compound of Formula (III):



(III),

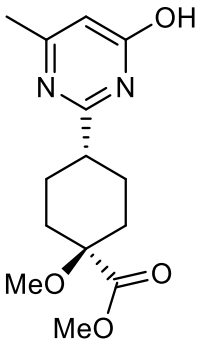
or a salt thereof; and

(b) reacting a compound of Formula (III) with alkyl acetoacetate, thereby producing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (IV) having a greater amount of the *cis* isomer, Formula (IVa):



(IVa),

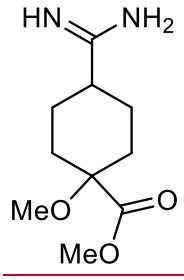
or a salt thereof, as compared to the *trans* isomer, Formula (IVb):



(IVb)

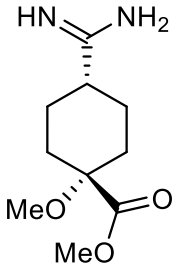
or a salt thereof.

[0005m] In a further aspect of the present disclosure, there is provided a process of preparing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (III) or a salt thereof with an increased ratio of the *cis* isomer to the *trans* isomer:



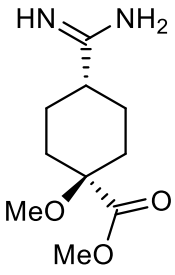
(III),

wherein the *cis* isomer is a compound of Formula (IIIa):



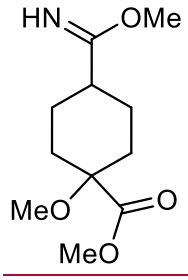
(IIIa),

or a salt thereof and the *trans* isomer is a compound of Formula (IIIb):



(IIIb),

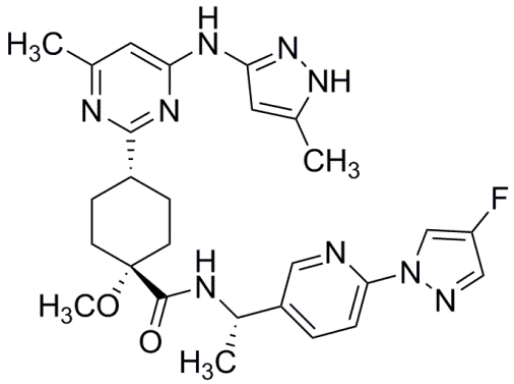
or a salt thereof, comprising reacting a compound of Formula (II):



(II),

or a salt thereof with an ammonium source in the presence of a solvent, thereby producing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (III) or a salt thereof with increased ratio of the *cis* isomer to the *trans* isomer.

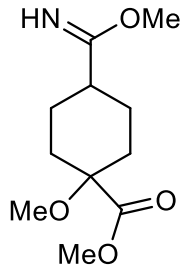
[0005n] In another aspect of the present disclosure, there is provided a process of preparing a compound of Formula (X):



(X),

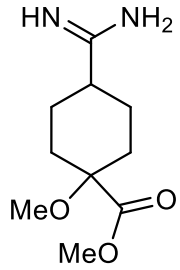
or a salt thereof, comprising the steps of:

(a) reacting a compound of Formula (II):



(II),

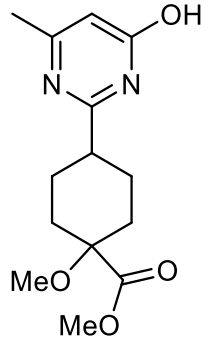
or a salt thereof with an ammonium source in the presence of a solvent, thereby producing a compound of Formula (III):



(III),

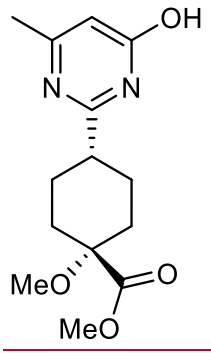
or a salt thereof;

(b) reacting a compound of Formula (III) with alkyl acetoacetate, thereby producing an isomeric mixture of a compound of Formula (IV):



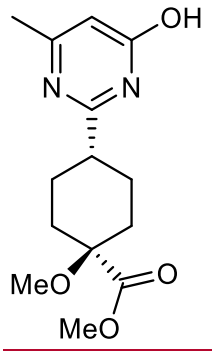
(IV),

or a salt thereof, wherein the isomeric mixture of the compound of Formula (IV) has a greater amount of the *cis* isomer, Formula (IVa):



(IVa),

or a salt thereof, as compared to the *trans* isomer, Formula (IVb):

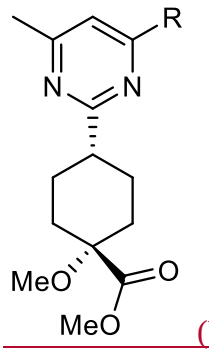


(IVb),

or a salt thereof;

(c) purifying the isomeric mixture of the compound of Formula (IV) or a salt thereof to obtain the compound of Formula (IVa) or a salt thereof;

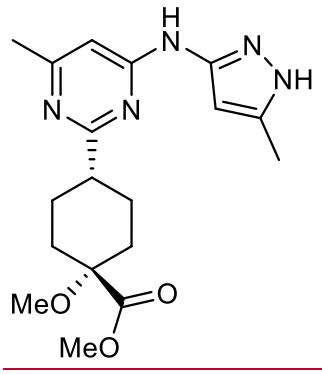
(d) reacting the compound of Formula (IVa) or a salt thereof with an activating agent, thereby providing a compound of Formula (V-1a):



(V-1a),

or a salt thereof;

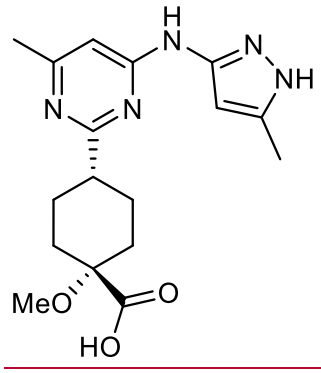
(e) reacting the compound of Formula (V-1a) or a salt thereof with 5-methyl-3-pyrazolamine, thereby providing a compound of Formula (VI):



(VI);

or a salt thereof;

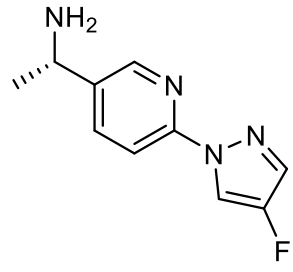
(f) reacting the compound of Formula (VI) or a salt thereof with a base, thereby providing a compound of Formula (VII):



(VII),

or a salt thereof;

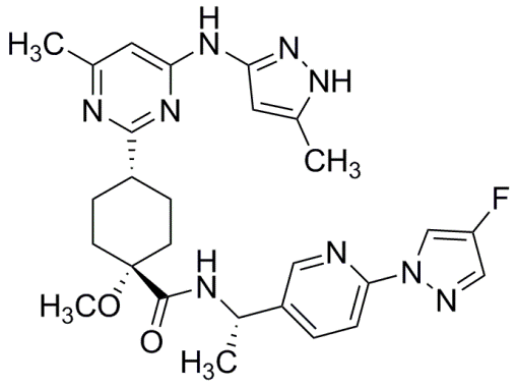
(g) reacting the compound of Formula (VII) or a salt thereof with a compound of Formula (VIII):



(VIII),

or a salt thereof, thereby providing the compound of Formula (X) or a salt thereof.

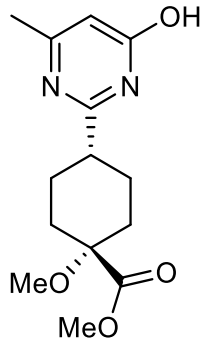
[0005o] In a further aspect of the present disclosure, there is provided a process of preparing a compound of Formula (X):



(X),

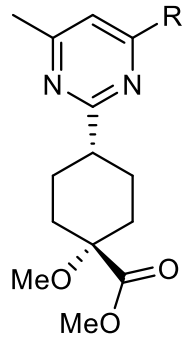
or a salt thereof, comprising the steps of:

(a) reacting a compound of Formula (IVa):



(IVa),

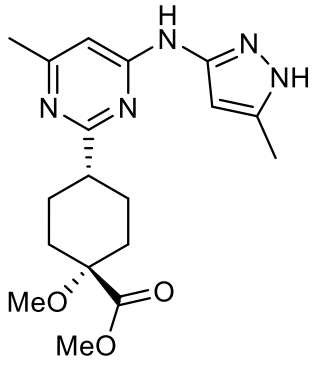
or a salt thereof with an activating agent, thereby providing a compound of Formula (V-1a):



(V-1a),

or a salt thereof, wherein R is an activating group;

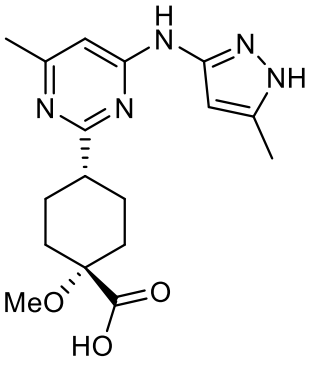
(b) reacting the compound of Formula (V-1a) or a salt thereof with 5-methyl-3-pyrazolamine, thereby providing a compound of Formula (VI):



(VI),

or a salt thereof;

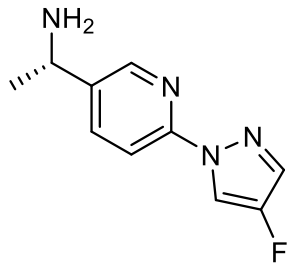
(c) reacting the compound of Formula (VI) or a salt thereof with a base, thereby providing a compound of Formula (VII):



(VII),

or a salt thereof; and

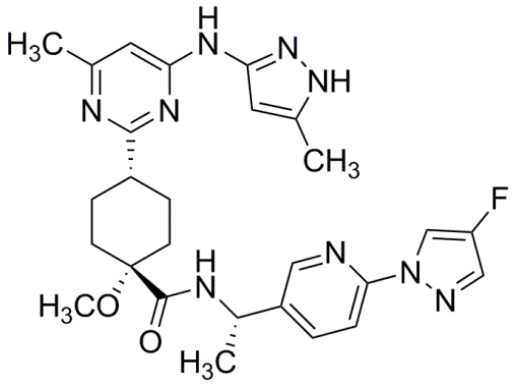
(d) reacting a compound of Formula (VII) or a salt thereof with a compound of Formula (VIII):



(VIII),

or a salt thereof, thereby providing a salt of a compound of Formula (X).

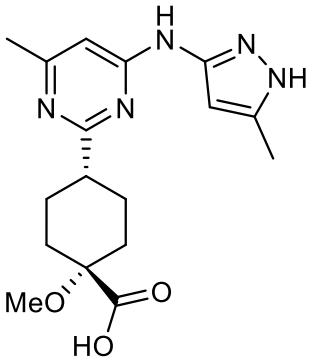
[0005p] In another aspect of the present disclosure, there is provided a process of preparing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (X) having a majority of the *cis* isomer configuration:



(X),

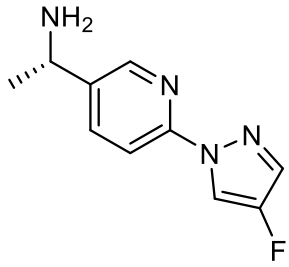
the process comprising:

reacting a compound of Formula (VII):



(VII),

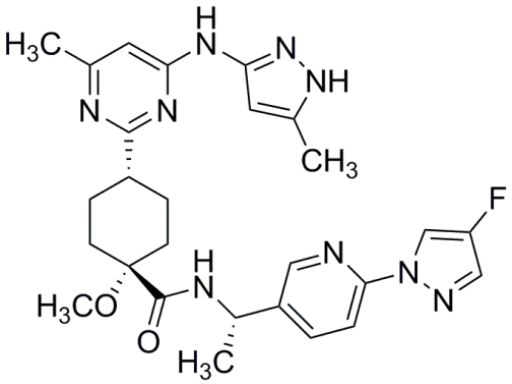
or a salt thereof, with a compound of Formula (VIII):



(VIII),

or a salt thereof, thereby providing a composition comprising a mixture of *cis* and *trans* isomers of the compound of Formula (X) having a majority of a *cis* isomer configuration.

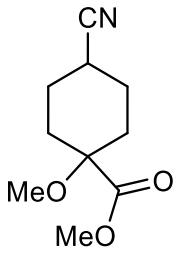
[0005q] In a further aspect of the present disclosure, there is provided a geometric isomeric mixture comprising a compound of Formula (X):



(X),

prepared with a process of claim 45 or 46, wherein the geometric isomer mixture has a *cis:trans* molar ratio of from about 4:1 to about 99:1.

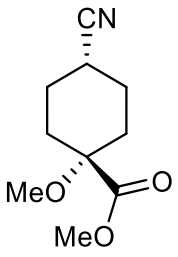
[0006] In one ~~aspect~~example, the present disclosure provides a compound of Formula (I):



(I),

or a salt thereof.

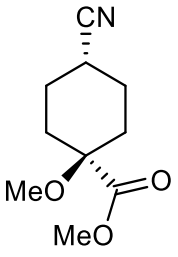
[0007] The compound of Formula (I) is a compound of Formula (Ia):



(Ia),

or a salt thereof.

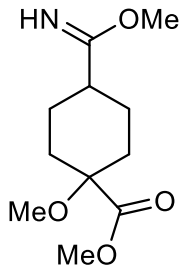
[0008] The compound of Formula (I) is a compound of Formula (Ib):



(Ib),

or a salt thereof.

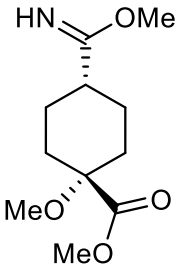
[0009] In another ~~aspect~~example, the present disclosure provides a compound of Formula (II):



(II),

or a salt thereof.

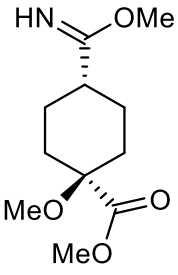
[0010] The compound of Formula (II) is a compound of Formula (IIa):



(IIa),

or a salt thereof.

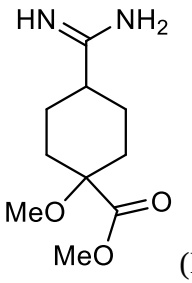
[0011] The compound of Formula (II) is a compound of Formula (IIb):



(IIb),

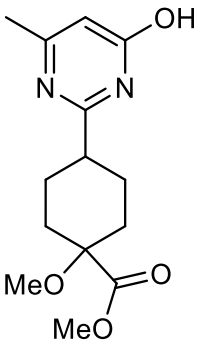
or a salt thereof.

[0012] The present disclosure provides, in part, a compound of Formula (III):



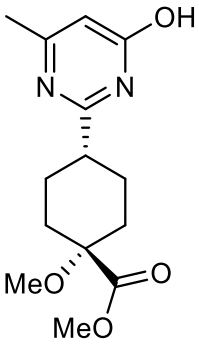
(III),

or a salt thereof.



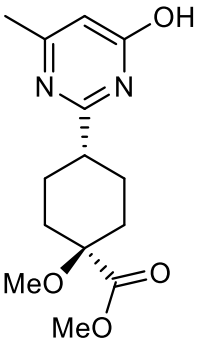
(IV),

or a salt thereof, wherein the *cis* isomer is a compound of Formula (IVa):



(IVa),

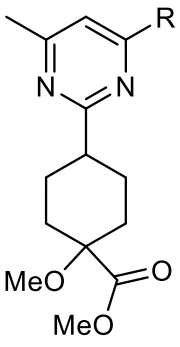
or a salt thereof and the *trans* isomer is a compound of Formula (IVb):



(IVb),

or a salt thereof, wherein the ratio of the *cis* isomer to the *trans* isomer is greater than or equal to about 4 to 1.

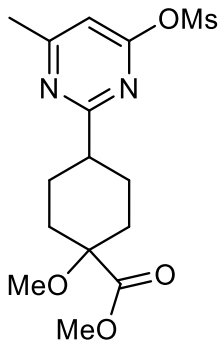
[0019] In another ~~aspect~~example, the present disclosure provides a compound of Formula (V-1):



(V-1),

or a salt thereof, wherein R is an activating group.

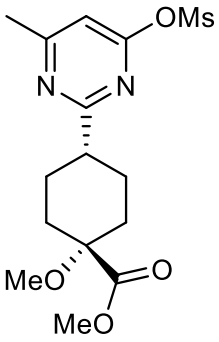
[0020] In some ~~embodiment~~examples, the compound of Formula (V-1) is a compound of Formula (V):



(V),

or a salt thereof.

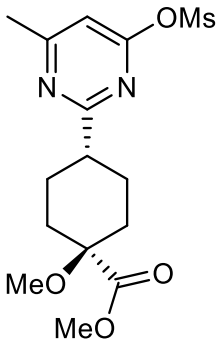
[0021] The compound of Formula (V) is a compound of Formula (Va):



(Va),

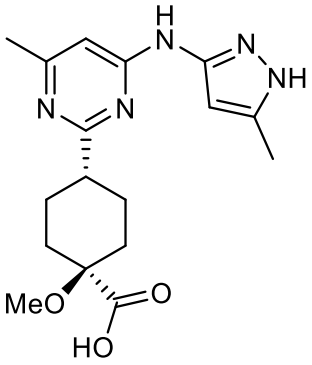
or a salt thereof.

[0022] The compound of Formula (V) is a compound of Formula (Vb):



(Vb),

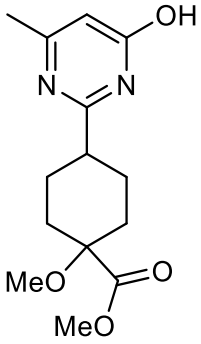
or a salt thereof.



(VIIa),

or a salt thereof.

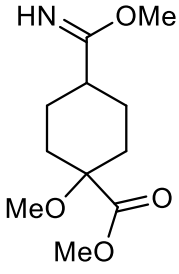
[0026] In another ~~aspect~~example, provided herein is a process of preparing a composition comprising a mixture of *cis* and *trans* isomers of a compound of Formula (IV):



(IV),

or a salt or a tautomer thereof, wherein the process comprises:

(a) reacting a compound of Formula (II):



(II),

or a salt thereof with an ammonium source in the presence of a solvent, thereby producing a compound of Formula (III):