

INHIBITORS OF RET

This invention relates to inhibitors of RET that are active against wild-type RET and its resistant mutants.

CLAIM OF PRIORITY

5 This application claims priority from U.S.S.N. 62/249,784, filed November 2, 2105, and U.S.S.N. 62/367,960, filed July 28, 2016, each of which is incorporated herein in its entirety.

BACKGROUND

10 RET (rearranged during transfection) is a receptor tyrosine kinase that activates multiple downstream pathways involved in cell proliferation and survival. RET fusions are implicated in several cancers including papillary thyroid carcinoma and non-small cell lung cancer. A genomics analysis on the landscape of kinase fusions identified RET fusions in breast and colon cancer patient samples, providing therapeutic rationale for the use of RET inhibitors in multiple patient subpopulations.

15 The identification of RET fusions as drivers in some cancers prompted the use of approved multi-kinase inhibitors with RET inhibitory activity to treat patients whose tumors express a RET fusion protein. However, these drugs cannot always be dosed at the levels required to sufficiently inhibit RET due to toxicities that result from inhibition of targets other than RET. Further, one of the greatest challenges in treating cancer is the ability of tumor cells to become resistant to therapy. Kinase reactivation via mutation is a common mechanism of resistance. When resistance occurs, the patient's treatment options are often very limited, and the cancer progresses, unchecked, in most instances. There is thus a need for compounds that inhibit RET, as well as its resistant mutants.

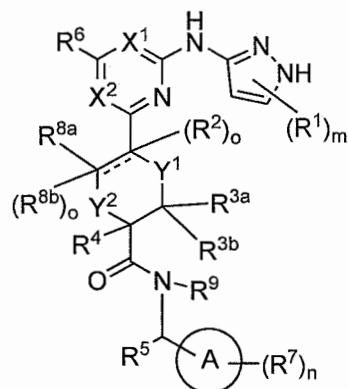
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SUMMARY

25 The present disclosure provides inhibitors of RET and RET mutants, *e.g.*, RET resistant mutants (as defined herein), for example, inhibitors of structural formula (I) and pharmaceutically acceptable salts and compositions thereof. The present disclosure further provides methods of using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to inhibit the activity of RET or RET mutants in a cell or patient.

The present disclosure still further provides methods for using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to treat a subject suffering from a condition mediated by aberrant RET activity, *e.g.*, cancer.

The present disclosure features a compound of structural formula (A) or a pharmaceutically acceptable salt thereof:

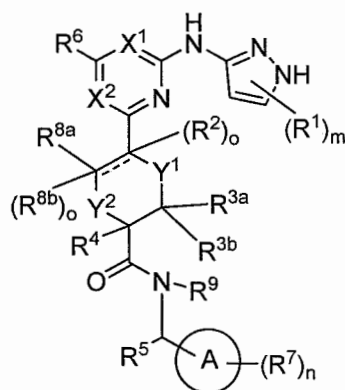


(A)

wherein each of ring A, X¹, X², Y¹, Y², R¹, R², R^{3a}, R^{3b}, R⁴, R⁵, R⁶, R⁷, R^{8a}, R^{8b}, R⁹, m, n, o and

“==” is defined as described herein.

In one aspect, the present disclosure provides a compound having the formula (A):



(A),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is an aryl or heteroaryl ring;

each of X^1 and X^2 is independently selected from N and $C(R^6)$;

each of Y^1 and Y^2 is independently selected from $-CH_2-$ and $-O-$, wherein no more than one of Y^1 or Y^2 is $-O-$;

each R^1 and each R^7 is independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R$, $-OC(O)R$, $-C(O)OR$, $-(C_1-C_6 \text{ alkylene})-C(O)R$, $-SR$, $-S(O)_2R$, $-S(O)_2-N(R)(R)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2R$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R)(R)$, $-N(R)(R)$, $-C(O)-N(R)(R)$, $-N(R)-C(O)R$, $-N(R)-C(O)OR$, $-(C_1-C_6 \text{ alkylene})-N(R)-C(O)R$, $-N(R)S(O)_2R$, and $-P(O)(R)(R)$, wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a , or two R^1 or two R^7 are taken together with the carbon atoms to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b ;

each of R^2 , R^{3a} , R^{3b} , R^4 , R^{8a} , and R^{8b} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, hydroxyl, C_1-C_6 heteroalkyl, and $-N(R)(R)$, wherein each alkyl, alkoxy, and heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each of R^5 and R^9 is independently selected from hydrogen, C_1-C_6 alkyl, and C_1-C_6 heteroalkyl, wherein each alkyl and heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R^6 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, and $-N(R)(R)$, wherein each alkyl, alkoxy, and heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each R is independently selected from hydrogen, hydroxyl, halo, thiol, C_1-C_6 alkyl, C_1-C_6 thioalkyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each alkyl, thioalkyl, alkoxy, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a , or 2 R together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b ;

each R^a and each R^b is independently selected from C_1-C_6 alkyl, halo, hydroxyl, C_1-C_6

heteroalkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, and cyano, wherein each alkyl, heteroalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R';

each R' is independently selected from C₁-C₆ alkyl, C₁-C₆ heteroalkyl, halo, hydroxyl, cycloalkyl, and cyano, or 2 R' together with the atom(s) to which they are attached form a

5 cycloalkyl or heterocyclyl ring;

== represents a single or double bond;

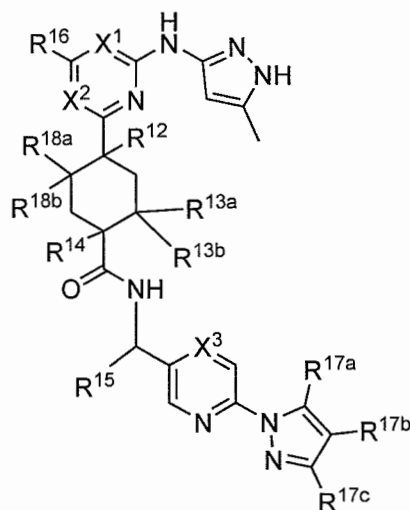
m is 0, 1, or 2;

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

each o is 0 when == is a double bond; and

10 each o is 1 when == is a single bond.

In another aspect, the present disclosure provides a compound having the formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

15 X¹ is selected from N, CH, and C(halo);

X² is selected from N and CH;

X³ is selected from N and CH;

R¹² is selected from hydrogen, hydroxyl, halo, and O-C₁-C₄ alkyl;

each of R^{13a}, R^{13b}, R^{18a}, and R^{18b} is independently selected from hydrogen and C₁-C₄

20 alkyl;

R¹⁴ is selected from hydrogen, C₁-C₄ alkyl, and O-C₁-C₄ alkyl;

R¹⁵ is selected from hydrogen and C₁-C₄ alkyl;

2b

R¹⁶ is selected from hydrogen and C₁-C₄ alkyl;

R^{17b} is selected from hydrogen and halo; and

each of R^{17a} and R^{17c} is independently selected from hydrogen and C₁-C₄ alkyl.

5 The present disclosure provides pharmaceutical compositions comprising a compound of structural formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure provides a pharmaceutical composition comprising: a compound as disclosed herein or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

10 In yet another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the treatment of a disease selected from non-small cell lung cancer, papillary thyroid carcinoma, medullary thyroid cancer, colorectal cancer, and multiple endocrine neoplasia.

15 The present disclosure provides a method for inhibiting RET activity in a cell or in a patient. In some embodiments, said method comprises the step of contacting the cell or administering to the patient a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

20 In another aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for inhibiting RET activity in a cell or in a patient.

The present disclosure provides a method for treating a subject suffering from a condition mediated by aberrant RET activity. In some embodiments, said method comprises administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

25 In a further aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from a condition mediated by aberrant RET activity.

The present disclosure provides a method for treating a subject who has developed resistance to a cancer treatment. In some embodiments, said method comprises

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administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

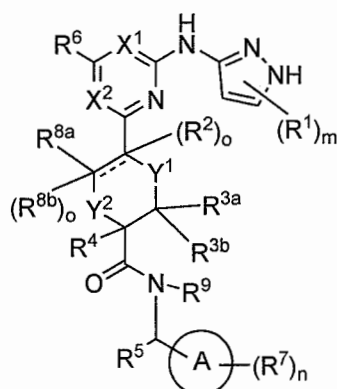
In another aspect, the present disclosure provides a use of a compound or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment.

EMBODIMENTS OF THE INVENTION

Compounds

In one aspect, the present invention features a compound having the structural formula

(A):



(A)

or a pharmaceutically acceptable salt thereof, wherein:

ring A is an aryl or heteroaryl ring;

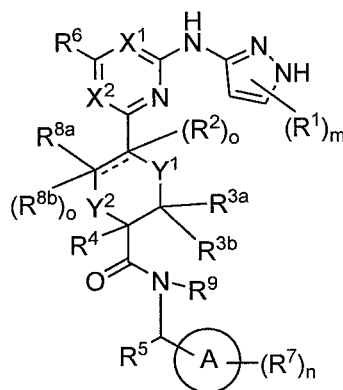
each of X^1 and X^2 is independently selected from N and $C(R^6)$;

each of Y^1 and Y^2 is independently selected from $-CH_2-$ and $-O-$, wherein no more than one of Y^1 or Y^2 is $-O-$;

each R^1 and each R^7 is independently selected from selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, halo, C_1-C_6 heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R$, $-OC(O)R$, $-C(O)OR$, $-(C_1-C_6$ alkylene)- $C(O)R$, $-SR$, $-S(O)_2R$, $-S(O)_2-N(R)(R)$, $-(C_1-C_6$ alkylene)- $S(O)_2R$, $-(C_1-C_6$ alkylene)- $S(O)_2-N(R)(R)$, $-N(R)(R)$, $-C(O)-N(R)(R)$, $-N(R)-C(O)R$, $-N(R)-C(O)OR$, $-(C_1-C_6$ alkylene)- $N(R)-C(O)R$, $-N(R)S(O)_2R$, and $-P(O)(R)(R)$; wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a ; or two R^1 or two

Claims:

1. A compound having the formula (A):



(A),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is an aryl or heteroaryl ring;

each of X^1 and X^2 is independently selected from N and $C(R^6)$;

each of Y^1 and Y^2 is independently selected from $-CH_2-$ and $-O-$, wherein no more than one of Y^1 or Y^2 is $-O-$;

each R^1 and each R^7 is independently selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, $-C(O)R$, $-OC(O)R$, $-C(O)OR$, $-(C_1-C_6 \text{ alkylene})-C(O)R$, $-SR$, $-S(O)_2R$, $-S(O)_2-N(R)(R)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2R$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R)(R)$, $-N(R)(R)$, $-C(O)-N(R)(R)$, $-N(R)-C(O)R$, $-N(R)-C(O)OR$, $-(C_1-C_6 \text{ alkylene})-N(R)-C(O)R$, $-N(R)S(O)_2R$, and $-P(O)(R)(R)$, wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a , or two R^1 or two R^7 are taken together with the carbon atoms to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b ;

each of R^2 , R^{3a} , R^{3b} , R^4 , R^{8a} , and R^{8b} is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, hydroxyl, C_1 - C_6 heteroalkyl, and $-N(R)(R)$, wherein each alkyl, alkoxy, and heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

each of R⁵ and R⁹ is independently selected from hydrogen, C₁-C₆ alkyl, and C₁-C₆ heteroalkyl, wherein each alkyl and heteroalkyl is independently substituted with 0-5 occurrences of R^a;

each R⁶ is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, C₁-C₆ heteroalkyl, and -N(R)(R), wherein each alkyl, alkoxy, and heteroalkyl is independently substituted with 0-5 occurrences of R^a;

each R is independently selected from hydrogen, hydroxyl, halo, thiol, C₁-C₆ alkyl, C₁-C₆ thioalkyl, C₁-C₆ alkoxy, C₁-C₆ heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each alkyl, thioalkyl, alkoxy, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a, or 2 R together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b;

each R^a and each R^b is independently selected from C₁-C₆ alkyl, halo, hydroxyl, C₁-C₆ heteroalkyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, and cyano, wherein each alkyl, heteroalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R['];

each R['] is independently selected from C₁-C₆ alkyl, C₁-C₆ heteroalkyl, halo, hydroxyl, cycloalkyl, and cyano, or 2 R['] together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring;

== represents a single or double bond;

m is 0, 1, or 2;

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

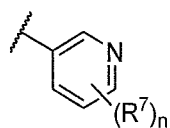
each o is 0 when == is a double bond; and

each o is 1 when == is a single bond.

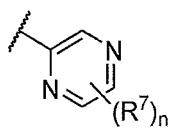
2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:
m is 1;
R¹ is located at the 5-position; and

R¹ is C₁-C₄ alkyl optionally substituted with 0-3 occurrences of R^a.

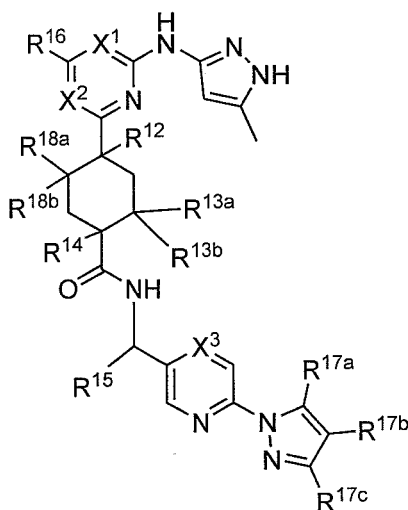
3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R² is selected from hydrogen, hydroxyl, halo, and C₁-C₄ alkoxy.
4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein each of R^{3a}, R^{3b}, R^{8a}, and R^{8b} is independently selected from hydrogen and C₁-C₄ alkyl optionally substituted with 0-3 occurrences of R^a.
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein at least one pair of R^{3a} and R^{3b} or R^{8a} and R^{8b} is simultaneously hydrogen.
6. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R⁴ is selected from hydrogen, C₁-C₄ alkyl, and C₁-C₄ alkoxy, wherein each alkyl portion of R⁴ is optionally substituted with 0-3 occurrences of R^a.
7. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen or C₁-C₄ alkyl optionally substituted with 0-3 occurrences of R^a.
8. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein each R⁶ is independently selected from hydrogen, halo, and C₁-C₄ alkyl optionally substituted with 0-3 occurrences of R^a.
9. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein ring A is a 6-membered monocyclic heteroaryl comprising at least one nitrogen ring atom.
10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein ring A is selected from



and



11. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:
n is 1; and
R⁷ is pyrazol-1-yl optionally substituted with 0-3 occurrences of R^a.
12. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R⁹ is hydrogen.
13. A compound having the formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

- X¹ is selected from N, CH, and C(halo);
- X² is selected from N and CH;
- X³ is selected from N and CH;
- R¹² is selected from hydrogen, hydroxyl, halo, and O-C₁-C₄ alkyl;
- each of R^{13a}, R^{13b}, R^{18a}, and R^{18b} is independently selected from hydrogen and C₁-C₄ alkyl;

R¹⁴ is selected from hydrogen, C₁-C₄ alkyl, and O-C₁-C₄ alkyl;

R¹⁵ is selected from hydrogen and C₁-C₄ alkyl;

R¹⁶ is selected from hydrogen and C₁-C₄ alkyl;

R^{17b} is selected from hydrogen and halo; and

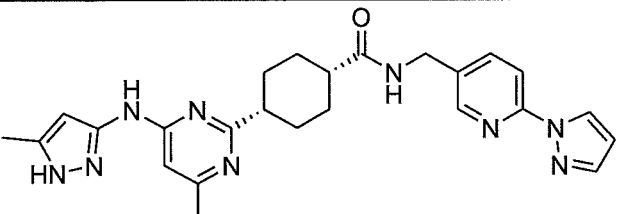
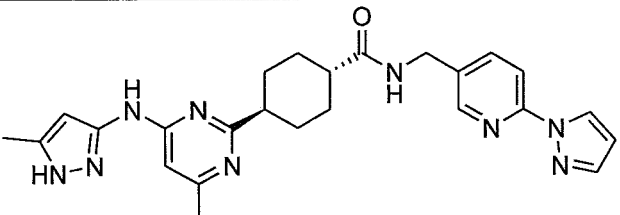
each of R^{17a} and R^{17c} is independently selected from hydrogen and C₁-C₄ alkyl.

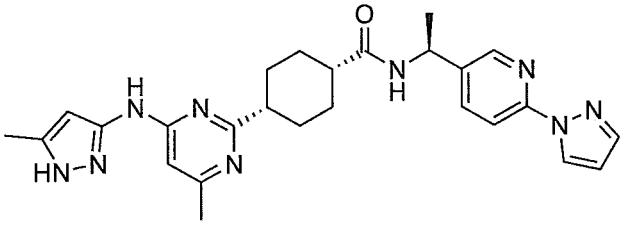
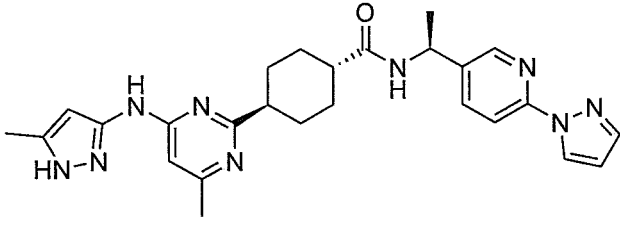
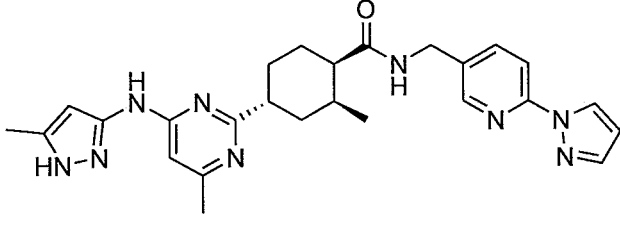
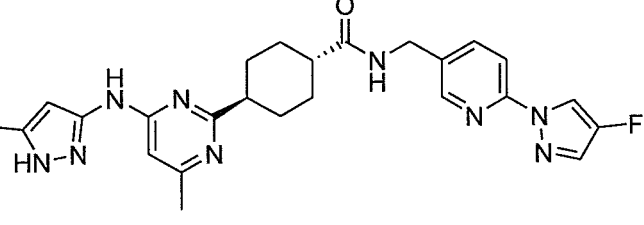
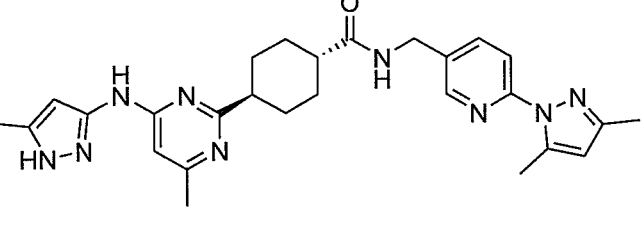
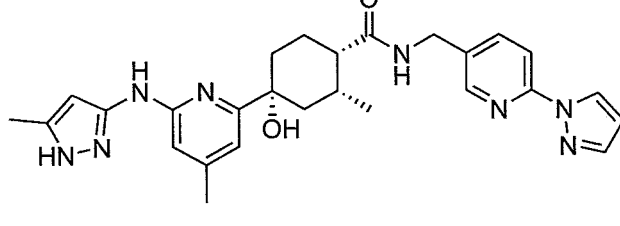
14. A pharmaceutical composition comprising:

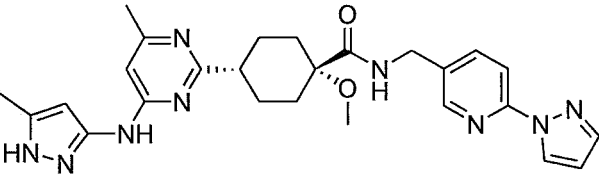
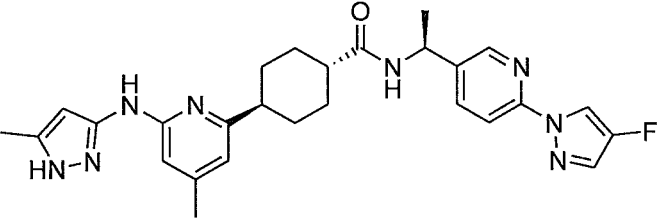
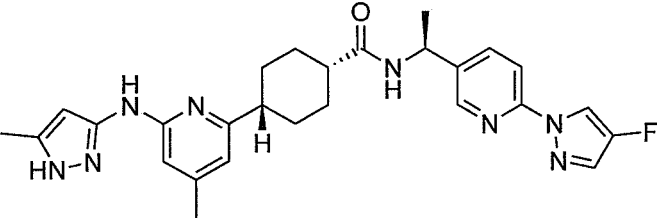
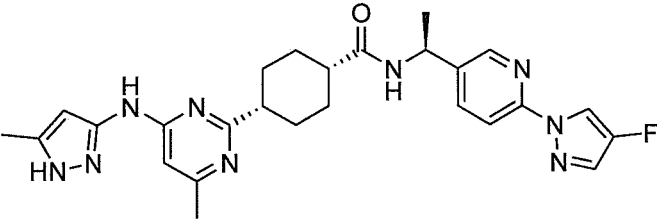
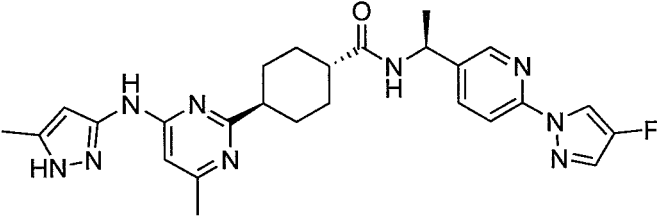
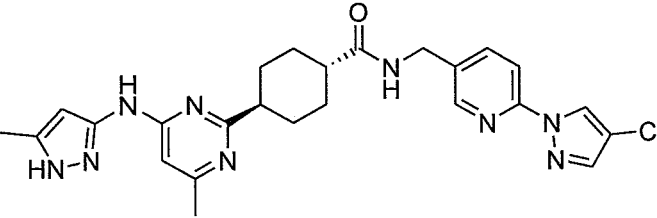
a compound of claim 1 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

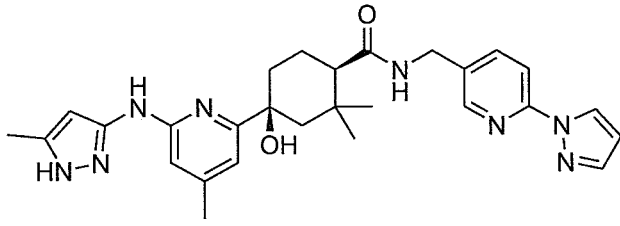
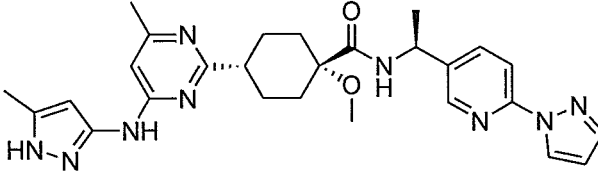
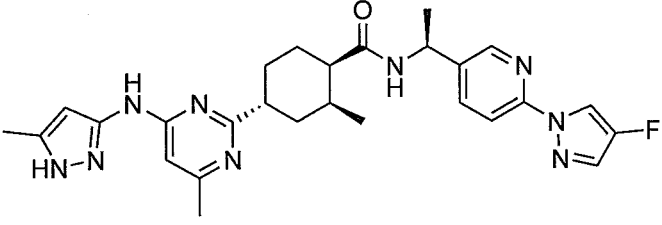
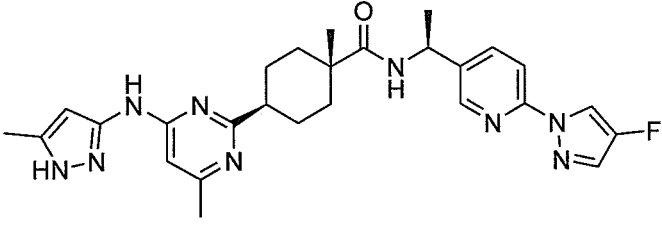
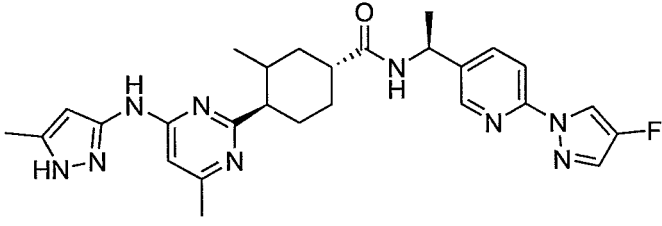
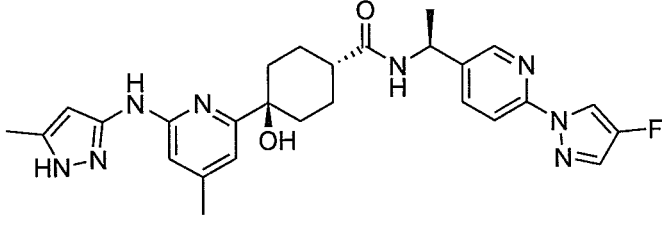
15. Use of a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for the treatment of a disease selected from non-small cell lung cancer, papillary thyroid carcinoma, medullary thyroid cancer, colorectal cancer, and multiple endocrine neoplasia.

16. A compound selected from:

Compound	Structure
100	
101	

Compound	Structure
102	
103	
104	
105	
106	
107	

Compound	Structure
108	
109	
110	
111	
112	
113	

Compound	Structure
114	
115	
116	
117	
118	
119	

Compound	Structure
120	
121	
122	
123	
124	
125	

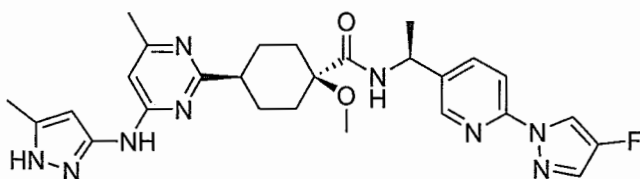
Compound	Structure
126	
127	
128	
129	
130	
131	

Compound	Structure
132	
133	
134	
135	
136	
137	
138	

Compound	Structure
139	
140	
141	
142	
143	
144	
145	

Compound	Structure
146	
147	
148	
149	
150	
151	

17. A compound selected from:



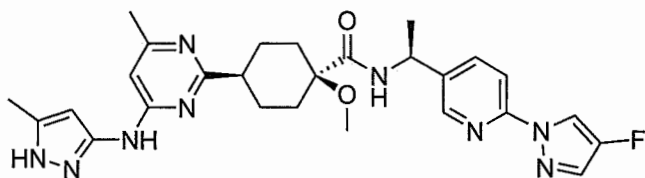
and pharmaceutically acceptable salts thereof.

18. A pharmaceutical composition comprising:

a compound of claim 17 or a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier.

19. Use of a therapeutically effective amount of a compound of claim 17 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease selected from non-small cell lung cancer, papillary thyroid carcinoma, medullary thyroid cancer, colorectal cancer, and multiple endocrine neoplasia.

20. A compound



21. Use of a compound of any one of claims 1 to 13, 16, 17, or 20 or a pharmaceutical composition of claim 14 or 18 in the manufacture of a medicament for inhibiting RET activity in a cell or in a patient.

22. Use of a compound of any one of claims 1 to 13, 16, 17, or 20 or a pharmaceutical composition of claim 14 or 18 in the manufacture of a medicament for treating a subject suffering from a condition mediated by aberrant RET activity.

23. Use of a compound of any one of claims 1 to 13, 16, 17, or 20 or a pharmaceutical composition of claim 14 or 18 in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment.