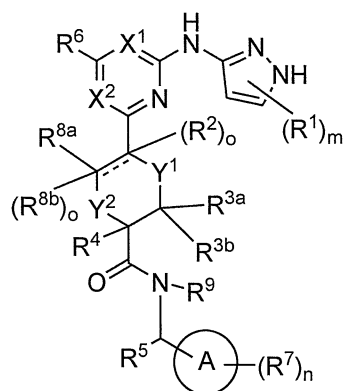


The present disclosure still further provides methods for using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to treat a subject suffering from a condition mediated by aberrant RET activity, *e.g.*, cancer.

The present disclosure features a compound of structural formula (A) or a

5 pharmaceutically acceptable salt thereof:



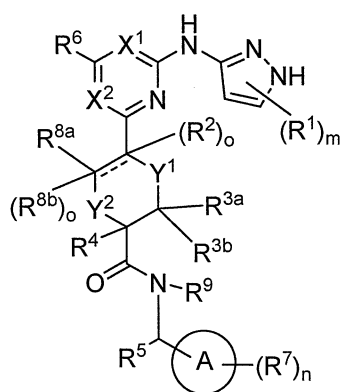
(A)

wherein each of ring A, X<sup>1</sup>, X<sup>2</sup>, Y<sup>1</sup>, Y<sup>2</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8a</sup>, R<sup>8b</sup>, R<sup>9</sup>, m, n,

o and

10 “---” is defined as described herein.

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



(A),

15 or a pharmaceutically acceptable salt thereof, wherein:

ring A is a 6-membered monocyclic heteroaryl ring comprising at least one nitrogen ring atom;

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  $R^1$  is independently selected from  $C_1-C_6$  alkyl,  $C_2-C_6$  alkenyl,  $C_2-C_6$  alkynyl,  $C_1-C_6$

5 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  $R^1$  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  $R^b$ ;

$R^7$  is heteroaryl substituted with 0-3 occurrences of  $R^b$ ;

15 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  $R^a$ ;

20 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  $R^b$ ;

30  $R^b$ ;

each R<sup>a</sup> and each R<sup>b</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, halo, hydroxyl, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, cycloalkyl, heterocyclyl, and cyano, wherein each alkyl, heteroalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R<sup>'</sup>;

each R<sup>'</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, halo, hydroxyl, cycloalkyl, and cyano, or 2 R<sup>'</sup> together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring;

== represents a single or double bond;

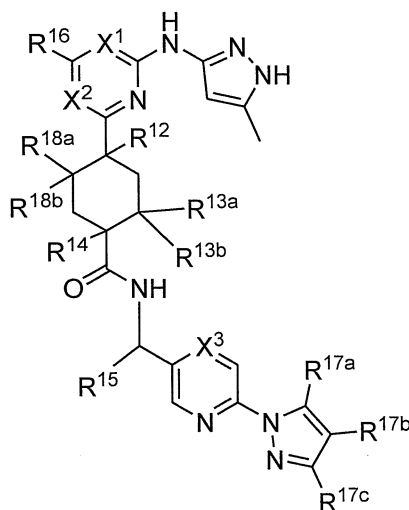
m is 0, 1, or 2;

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.

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



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X<sup>1</sup> is selected from N, CH, and C(halo);

X<sup>2</sup> is selected from N and CH;

X<sup>3</sup> is selected from N and CH;

R<sup>12</sup> is selected from hydrogen, hydroxyl, halo, and O-C<sub>1</sub>-C<sub>4</sub> alkyl;

each of R<sup>13a</sup>, R<sup>13b</sup>, R<sup>18a</sup>, and R<sup>18b</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>14</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and O-C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>15</sup> is selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>16</sup> is selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>17b</sup> is selected from hydrogen and halo; and

each of R<sup>17a</sup> and R<sup>17c</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> 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.

10        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.

15        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.

      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        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.

25        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.

      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

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  
5 a subject who has developed resistance to a cancer treatment.

In another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from non-small cell lung cancer.

10 In a yet another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from papillary thyroid cancer.

15 In a further aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from medullary thyroid cancer.

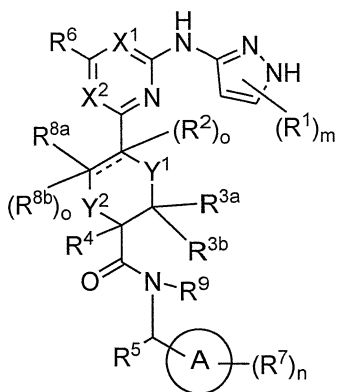
20 In another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from colorectal cancer.

25 In another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a subject suffering from multiple endocrine neoplasia.

## **EMBODIMENTS OF THE INVENTION**

### Compounds

30 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;

5 each of X<sup>1</sup> and X<sup>2</sup> is independently selected from N and C(R<sup>6</sup>);

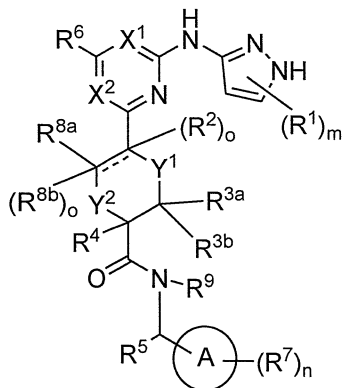
each of Y<sup>1</sup> and Y<sup>2</sup> is independently selected from -CH<sub>2</sub>- and -O-, wherein no more than one of Y<sup>1</sup> or Y<sup>2</sup> is -O-;

each R<sup>1</sup> and each R<sup>7</sup> is independently selected from selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, -C(O)R, -OC(O)R, -C(O)OR, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-C(O)R, -SR, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>-N(R)(R), -(C<sub>1</sub>-C<sub>6</sub> alkylene)-S(O)<sub>2</sub>R, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-S(O)<sub>2</sub>-N(R)(R), -N(R)(R), -C(O)-N(R)(R), -N(R)-C(O)R, -N(R)-C(O)OR, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-N(R)-C(O)R, -N(R)S(O)<sub>2</sub>R, and -P(O)(R)(R); wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and

15 heterocyclylalkyl is independently substituted with 0-5 occurrences of R<sup>a</sup>; or two R<sup>1</sup> or two

Claims:

1. A compound having the formula (A):



(A),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is a 6-membered monocyclic heteroaryl ring comprising at least one nitrogen ring atom;

each of X<sup>1</sup> and X<sup>2</sup> is independently selected from N and C(R<sup>6</sup>);

each of Y<sup>1</sup> and Y<sup>2</sup> is independently selected from -CH<sub>2</sub>- and -O-, wherein no more than one of Y<sup>1</sup> or Y<sup>2</sup> is -O-;

each R<sup>1</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, -C(O)R, -OC(O)R, -C(O)OR, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-C(O)R, -SR, -S(O)<sub>2</sub>R, -S(O)<sub>2</sub>-N(R)(R), -(C<sub>1</sub>-C<sub>6</sub> alkylene)-S(O)<sub>2</sub>R, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-S(O)<sub>2</sub>-N(R)(R), -N(R)(R), -C(O)-N(R)(R), -N(R)-C(O)R, -N(R)-C(O)OR, -(C<sub>1</sub>-C<sub>6</sub> alkylene)-N(R)-C(O)R, -N(R)S(O)<sub>2</sub>R, 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<sup>a</sup>, or two R<sup>1</sup> 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<sup>b</sup>;

R<sup>7</sup> is heteroaryl substituted with 0-3 occurrences of R<sup>b</sup>;

each of R<sup>2</sup>, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>4</sup>, R<sup>8a</sup>, and R<sup>8b</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, hydroxyl, C<sub>1</sub>-C<sub>6</sub> heteroalkyl, and -N(R)(R), wherein each alkyl, alkoxy, and heteroalkyl is independently substituted with 0-5 occurrences of R<sup>a</sup>;

R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 0-3 occurrences of R<sup>a</sup>.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R<sup>2</sup> is selected from hydrogen, hydroxyl, halo, and C<sub>1</sub>-C<sub>4</sub> alkoxy.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein each of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>8a</sup>, and R<sup>8b</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 0-3 occurrences of R<sup>a</sup>.

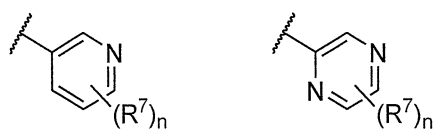
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein at least one pair of R<sup>3a</sup> and R<sup>3b</sup> or R<sup>8a</sup> and R<sup>8b</sup> is simultaneously hydrogen.

6. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R<sup>4</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy, wherein each alkyl portion of R<sup>4</sup> is optionally substituted with 0-3 occurrences of R<sup>a</sup>.

7. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 0-3 occurrences of R<sup>a</sup>.

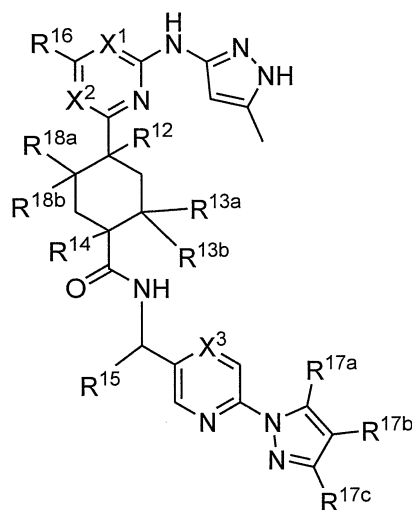
8. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein each R<sup>6</sup> is independently selected from hydrogen, halo, and C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with 0-3 occurrences of R<sup>a</sup>.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein ring A is selected from



and

10. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:  
n is 1; and  
R<sup>7</sup> is pyrazol-1-yl optionally substituted with 0-3 occurrences of R<sup>a</sup>.
11. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R<sup>9</sup> is hydrogen.
12. A compound having the formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X<sup>1</sup> is selected from N, CH, and C(halo);

X<sup>2</sup> is selected from N and CH;

X<sup>3</sup> is selected from N and CH;

R<sup>12</sup> is selected from hydrogen, hydroxyl, halo, and O-C<sub>1</sub>-C<sub>4</sub> alkyl;

each of R<sup>13a</sup>, R<sup>13b</sup>, R<sup>18a</sup>, and R<sup>18b</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>14</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and O-C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>15</sup> is selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>16</sup> is selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>17b</sup> is selected from hydrogen and halo; and

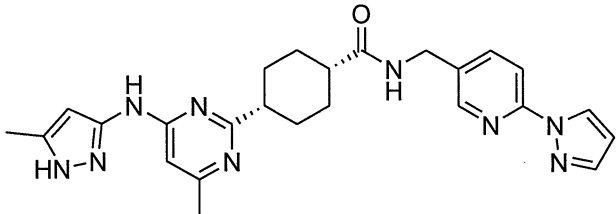
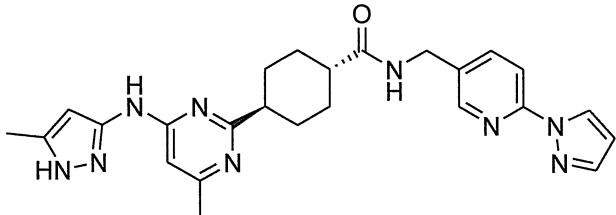
each of R<sup>17a</sup> and R<sup>17c</sup> is independently selected from hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl.

13. A pharmaceutical composition comprising:

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

14. 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.

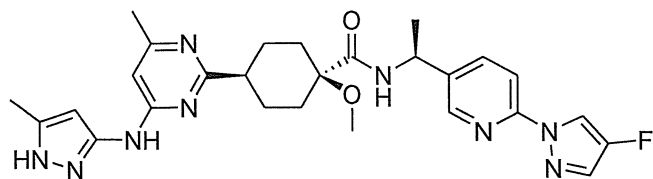
15. A compound selected from:

| Compound | Structure                                                                            |
|----------|--------------------------------------------------------------------------------------|
| 100      |  |
| 101      |  |

| Compound | Structure |
|----------|-----------|
| 146      |           |
| 147      |           |
| 148      |           |
| 149      |           |
| 150      |           |
| 151      |           |

, or a pharmaceutically acceptable salt thereof.

16. A compound of the following structure:



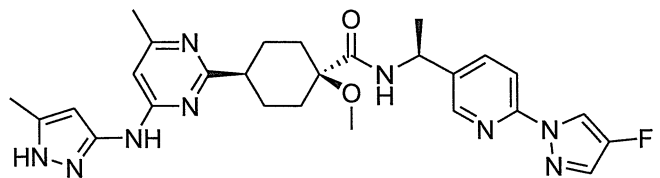
or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising:

a compound of claim 16 or a pharmaceutically acceptable salt thereof; and  
a pharmaceutically acceptable carrier.

18. Use of a therapeutically effective amount of a compound of claim 16 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.

19. A compound of the following structure:



20. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutical composition of claim 13 or 17 in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment.

21. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 14 or 17 in the manufacture of a medicament for treating a subject suffering from non-small cell lung cancer.
22. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 14 or 17 in the manufacture of a medicament for treating a subject suffering from papillary thyroid cancer.
23. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 14 or 17 in the manufacture of a medicament for treating a subject suffering from medullary thyroid cancer.
24. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 14 or 17 in the manufacture of a medicament for treating a subject suffering from colorectal cancer.
25. Use of a compound of any one of claims 1 to 12, 15, 16, or 19 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 14 or 17 in the manufacture of a medicament for treating a subject suffering from multiple endocrine neoplasia.